EXECUTIVE FUNCTION AND COPING IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

By

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To my husband Bryan, for everything.

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CHAPTER I

INTRODUCTION

Although its base rate is low compared to many other childhood diseases, cancer remains the leading cause of disease-related death of children in the United States. Approximately 1,560 children are expected to die from cancer this year, and an estimated 9,500 children under the age of 14 will receive a new cancer diagnosis (American Cancer Society, 2006). Acute lymphocytic leukemia (ALL) is the most common form of childhood cancer, accounting for nearly one-third of all diagnoses (American Cancer Society, 2006). An invariably fatal disease prior to 1960 (Mulhern, 1994), ALL now has a five-year survival rate of over 70% owing to the introduction and ongoing modification of powerful treatment protocols, which not only destroy leukemic cells in the bone marrow, organs, and cerebrospinal fluid (CSF) but also prevent disease relapse in the central nervous system (i.e., CNS prophylaxis; Smith, Ries, Gurney, & Ross, 2004).

As a result of these advances in treatment, the majority of children diagnosed with ALL are living well into adulthood, and the issue of managing the long-term sequelae of treatment and preserving quality of life of childhood ALL patients and survivors has become a major focus of research and clinical practice. Known long-term effects of treatment for childhood ALL can include hormone deficiencies, infertility, pulmonary fibrosis and inflammation, kidney disease, osteopenia, cardiac complications, dental abnormalities, and even the development of second cancers (American Cancer Society, 2006). It is no surprise that the Childhood Cancer Survivorship Study (CCSS), a

multicenter cohort study of the late effects of childhood cancer treatment, found that adult survivors of childhood ALL reported experiencing significantly more overall physical and mental health problems, activity limitations, and functional impairment compared to adult siblings with no history of cancer (Ness et al., 2005; Hudson et al., 2003; See Robison et al., 2005 for a review).

One important long-term consequence of ALL treatment that has been observed is impaired neurocognitive functioning. Declines in overall intellectual ability (e.g., Mulhern, Ochs, & Fairclough, 1992; see Cousens, Waters, Said, & Stevens, 1988 for early meta-analytic review), academic performance (e.g., Anderson et al., 2000), memory and learning (e.g., Hill et al., 1997), attention and concentration (e.g., Lockwood, Bell, & Colegrove, 1999), information processing speed (Cousens et al., 1991), visuospatial skill (e.g., Espy et al., 2001), psychomotor functioning (e.g., Kaleita et al., 1999), executive functioning (e.g., Anderson et al., 1997) and language skills (e.g., Buttsworth, Murdoch, & Ozanne, 1993) are among the adverse neurocognitive outcomes reported in the literature. A recently published meta-analytic review of the literature on the neurocognitive effects of treatment for childhood ALL found that when compared to control groups composed of healthy peers, siblings, or children treated for solid tumors or other chronic illness, ALL survivors experienced significant declines in both global and specific domains of neurocognitive function (Campbell et al., in press). The effect sizes ranged from small to moderate (g = -.34 to -.71) and were in the negative direction, indicating consistent deficits for groups of children treated for ALL across all nine neurocognitive domains assessed: Overall Cognitive Functioning (which includes scores on measures of verbal, performance, and full scale intelligence), Academic Achievement

(which includes Reading, Arithmetic, and Spelling Achievement), Attention, Executive Function, Verbal Memory, Visuospatial Memory, Visuospatial Skill, Psychomotor Skill, and Information Processing Speed.

Impairment in cognitive development and function holds clear implications for disruption in academic achievement and learning. However, cognitive impairments as a result of cancer treatment may also have ramifications for social and emotional development. Specifically, the current study focused on the broad higher order neurocognitive domain of executive function, as it has been shown to underlie emotion regulation and the utilization of adaptive coping mechanisms in children (Copeland & Compas, 2007). If this is indeed the case, then it would be expected that impaired executive function as a result of ALL treatment could delay the development of or erode previously developed skills needed to regulate emotions and cope with stressful situations. Further, because children who are unable to appropriately respond to stressful situations are considered to be at higher risk for developing symptoms of psychopathology (Compas et al. 2001), it follows that an indirect consequence of ALL treatment could be the onset or increase in emotional and behavioral problems in survivors of childhood cancer. This study examined the links among executive function, coping strategies, and emotional and behavioral outcomes, in children and adolescents who have completed treatment for ALL.

Before going on to describe the current study, I first provide an overview of basic information on childhood ALL and its treatment, as well as a summary of the neurophysiological and neurocognitive changes associated with childhood ALL treatment. I then proceed to discuss the model of coping that is employed in the proposed

study and further explain its relation to executive function and self-regulation. Lastly, I state the hypotheses and describe the method and results of the present study.

Pediatric ALL: Disease and Treatment Overview

Approximately 75% of all childhood leukemia diagnoses are acute lymphocytic leukemia (ALL), a disease in which immature lymphocytes (i.e., white blood cells) rapidly proliferate and accrue in the bone marrow and eventually spread to the blood, meninges, lymph nodes, testicles in boys, and vital organs throughout the body (National Cancer Institute, 2004). As leukemic cells accumulate, the cells that typically carry oxygen through the body (red blood cells), clot blood (platelets), and fight infection (normal white blood cells) are crowded out of the bone marrow and are unable to carry out their normal functions properly. Consequently, the most common signs and symptoms children with ALL present with include bruising, bleeding, pallor, fatigue, fever, bone pain, and anemia. While these symptoms and an abnormal blood cell count may be suggestive of the disease, a bone marrow sample drawn from the hip or sternum is necessary to make a definitive diagnosis of ALL. In addition, cerebrospinal fluid (CSF) taken from the spine via lumbar puncture must also be tested to determine whether the disease has advanced to the CNS (National Cancer Institute, 2004).

Once a diagnosis of ALL has been made the risk for relapse is estimated in order to determine what is likely to be the most effective course of treatment. A number of factors are taken into account to determine prognosis, such as the child's age (children 2-10 years of age have better outcomes on average), sex (girls have higher remission and cure rates than boys), white blood cell count, certain genetic mutations (e.g., Philadelphia

chromosome), and the extent to which the disease has spread (National Cancer Institute, 2004). Children considered "high-risk" because they have a number of risk factors receive the most aggressive forms of treatment, which consequently are most likely to have adverse long-term effects, while children with a relatively good prognosis (i.e., "standard-risk") are spared the most toxic of therapies.

The current standard of care for the treatment of childhood ALL involves the administration of multiple chemotherapy drugs at specifically scheduled intervals over a period of two to three years. Treatment occurs in four phases. During the induction phase, remission of the disease is achieved by means of systemic chemotherapy (i.e., chemotherapy administered intravenously, intramuscularly, or orally), which destroys leukemic cells located in bone marrow, liver, spleen, and lymph nodes. However, because these drugs cannot adequately infiltrate the blood-brain barrier, occult leukemic cells may remain in the CSF. Treatment administered directly to the CNS (i.e., CNS prophylaxis) during the second phase of treatment is necessary to eradicate these cells and prevent future leukemia relapse in the CNS (National Cancer Institute, 2004). Next, children undergo consolidation or intensification, during which high-dose chemotherapy drugs are employed in order to wipe out any remaining leukemic cells in the body. The fourth stage of treatment is referred to as maintenance therapy. At this final stage patients are administered lower doses of chemotherapy drugs for approximately two to three years to prevent leukemia relapse (National Cancer Institute, 2004). While systemic therapies at various stages of treatment as well as the disease itself surely contribute to adverse long-term outcomes in survivors of childhood ALL, CNS

prophylaxis, which is discussed in the following section, may be the primary cause of neurocognitive sequelae.

Although only 3% of childhood ALL patients present with occult leukemic cells in the CSF at the time of diagnosis, more than 50% of patients will develop CNS involvement if they do not receive CNS prophylaxis (National Cancer Institute, 2004). Consequently, all children diagnosed with ALL receive treatment designed to eradicate present CNS involvement and to prevent leukemia from developing in the CNS, in an effort to maximize their chance for survival. For low- and standard-risk patients the drug methotrexate alone or in combination with other chemotherapy, including corticosteroids, is administered directly into the spinal fluid by means of a lumbar puncture (i.e., intrathecally). Until full-brain or cranial irradiation therapy (CRT) was identified as a major cause of neurocognitive sequelae, most children diagnosed with ALL also received CRT as a part of CNS prophylaxis. Due to its known toxicity in the developing brain, CRT is now reserved for children with CNS involvement at diagnosis, relapsed patients, and children at very high risk for relapse (Brown et al. 1996). Although most no longer receive CRT, children with ALL remain at risk for declines in neurocognitive functioning because intrathecal methotrexate, the standard CNS prophylactic treatment has also been deemed as neurotoxic based on the results of some previous studies (see Campbell et al., in press for review).

Corticosteroids are usually incorporated in standard treatment protocols for childhood ALL and other types of cancer. Because of their anti-inflammatory properties, corticosteroids target and destroy white blood cells, and in the case of ALL, leukemic cells. Prednisone and dexamethasone are the most commonly used steroids and are

administered in conjunction with vincristine and other chemotherapy drugs. Because it is better able to penetrate the blood-brain barrier as a CNS prophylactic agent, dexamethasone is thought to be superior to prednisone in its ability to prevent CNS relapse (e.g., Kaspers et al., 1996). However, some studies have shown that dexamethasone increases children's risk of developing long-term neurocognitive sequelae to a greater degree than prednisone and so use of dexamethasone in children has been hotly contested. In one of these studies, Waber and colleagues (2000) compared two ALL treatment groups: one received dexamethasone whereas the other received prednisone, both in conjunction to other modes of treatment as usual. Results showed that the dexamethasone group performed significantly more poorly on tests of reading and mathematical academic achievement, working memory, and visuospatial skill and memory even after other treatment differences or effects were taken into account (Waber et al., 2000). Clinical trials continue to be conducted to determine whether the benefits of dexamethasone outweigh its risks in comparison with prednisone.

Although the majority of children diagnosed with ALL are successfully treated, a small number of patients will experience a relapse of their disease. Many of these children will respond well to a second intensive course of chemotherapy and CRT; however, the few who relapse early on during their initial course of treatment or whose ALL recurs several times may require stem-cell transplantation (SCT). This procedure involves harvesting bone marrow or stem cells from the patient (i.e., autologous) or from a matched donor (i.e., allogenic). The child then undergoes high dose chemotherapy and sometimes full body irradiation in order to destroy all remaining leukemic cells; however, normal bone marrow and immune system cells are also killed in the process. After the

SCT is performed, the child must stay in an environment free of pathogens due to chemotherapy-induced immunosuppression and is given supportive therapies to compensate for their deficient normal cells. Many complications, such as graft-versus-host disease and life-threatening infections, can result from SCT. In addition, most children suffer painful acute symptoms (e.g., mucositis) and some will experience disabling or even life-threatening late effects (cataracts; organ damage). Given their exposure to more neurotoxic treatments for a longer duration, children who relapse or undergo SCT may also be at even greater risk for developing neurocognitive deficits than children who were successfully treated following initial diagnosis (see Copeland, 1992 for review; Cool, 1996). For that reason, patients who experienced relapse or underwent SCT were considered beyond the scope of the current study.

Neurophysiological and Neurocognitive Changes Associated with ALL Treatment

Research has estimated that 16%-52% of children treated for ALL have at least one brain abnormality detected by magnetic resonance imaging (MRI) and computerized cranial tomography (CCT) scans (e.g., Hertzberg et al., 1997, Porto et al., 2004). According to Hertzberg and colleagues (1997) there are four distinct types of brain changes associated with CNS prophylaxis, including leukoencephalopathy and subacute necrotizing leukomyelopathy, both of which involve destruction of white matter; mineralizing microangiopathy (i.e., calcifications); and secondary CNS tumors. Other studies have also identified enlargement of ventricles, cortical atrophy, and cerebrovascular problems (e.g., strokes; hemorrhage) as a result of ALL treatment (Paakko et al., 1994; Hertzberg et al. 1997; Porto et al., 2004). There is evidence that

these changes are transient and may be temporally related to the administration of certain treatments, such as intermediate- or high-dose methotrexate (e.g., Chu et al. 2003; Paakko et al. 1992); however, their functional consequences may be permanent. Although direct relationships between structural changes and neurocognitive functioning remain unclear, findings from imaging studies paired with current knowledge of normal brain development could provide insight into the underlying causes of specific deficits exhibited by childhood ALL survivors.

Currently, the most widely studied treatment-induced brain abnormality and possibly the one with the most significant neurocognitive implications is the degeneration of white matter and disruption of myelination. Oligodendrocytes, a type of glial cell, produce myelin, which insulates neural pathways in the central nervous system in order to speed the transmission of information throughout the brain. Myelination begins during gestation and continues through adolescence and into early adulthood (Luna & Sweeney, 2004). Thus, because the cells producing myelin, particularly in the frontal lobe and basal ganglia, are still developing throughout childhood and adolescence, it is likely that they are particularly vulnerable to treatments that are meant to target rapidly proliferating leukemic cells and are administered directly to the developing CNS.

The cerebral hemispheres eventually become densely packed with white matter tracts that provide connections among cortical and subcortical structures (Lezak, Howieson, & Loring, 2004). The ratio of white matter to gray matter is even greater in the right hemisphere where it is thought to be mainly involved in processing and integrating visuospatial information and novel stimuli, coordinating movement, emotional understanding and expression, among other nonverbal functions (Rourke,

1987; Goldberg & Costa, 1981). Consequently, the functions primarily conducted in the right hemisphere would logically be most severely affected by abnormal or damaged white matter and could result in signs and symptoms consistent with nonverbal learning disabilities (NVLD), including impairments in the following domains: psychomotor coordination, visuospatial ability, visual-motor integration, nonverbal reasoning, attention, mathematical achievement, social skills, and emotionality (Rourke & Tsatsanis, 1996; Picard & Rourke, 1995). Previous research studies have identified subtle deficits consistent with NLD syndrome in children treated for ALL, providing evidence that the white matter changes in the right hemisphere that occur as a result of CNS prophylaxis is indeed associated with specific neurocognitive sequelae (for review, see Picard & Rourke, 1995).

Results from several previous studies have also suggested that children treated for ALL experience problems with executive functioning (e.g., Anderson, Godber, Smibert, & Ekert, 1997; Espy et al., 2001; see Campbell et al., in press, for a meta-analytic review), the set of higher order cognitive processes that includes planning, mental flexibility, initiation of behavior, behavioral inhibition, goal-directed behavior, working memory, and attention (Lezak, Howieson, & Loring, 2004). Impaired executive functioning is usually associated with damage to the prefrontal cortex, which happens to be the last area of the brain to become fully myelinated. The gradual emergence of the executive functions parallels the process of myelination, with both processes continuing into adulthood. Thus, disruption of myelination or damage to white matter caused by CNS prophylaxis during childhood or adolescence could prevent or inhibit the normal development of executive functions. This theory has been supported by studies that have

found symptoms of attention deficit hyperactivity disorder (ADHD) in children who had received treatment for ALL, specifically decreased attention and working memory, as well as slowed information processing speed (e.g., Schatz et al. 2000). As might be expected given these treatment-induced symptoms, methylphenidate, the standard treatment for children with ADHD, has been shown to improve attention in long-term childhood ALL survivors (Mulhern et al. 2004).

To summarize, several types of neurophysiological changes have been identified in children treated for ALL via neuro-imaging techniques. However, demyelination and damage to white matter tracts appear to have the most likely functional implications based on research studies that have found impaired executive functioning and NLD-like deficits in ALL survivors. These, among other neurocognitive problems that have been found in previous research, may be experienced on some level by all ALL survivors, but some children appear to be more susceptible to such treatment effects. The next section will discuss putative demographic and medical variables that increase children's vulnerability for neurocognitive effects.

Risk Factors for Developing Neurocognitive Sequelae of Pediatric ALL

Several potential risk factors for developing neurocognitive impairment have been found in previous studies of children treated for ALL. First, young age at diagnosis, especially during the first year of life, is considered to be a major risk factor for neurocognitive sequelae. Infants are especially vulnerable to CNS involvement and relapse and are consequently given additional CNS prophylaxis to improve their prognosis. Therefore, it is thought that infant patients are at greater risk for long-term

neurocognitive sequelae given the neurotoxicity of treatment and a rapidly developing brain. However, contrary to this hypothesis, in a study of 30 children who were treated for ALL during the first year of life, an average of 5 years prior to testing, cognitive functioning as measured by the McCarthy Scales of Children's Abilities was found to fall well within the average range compared to normative data (Kaleita, Reaman, MacLean, Sather, & Whitt, 1999).

In contrast to the Kaleita et al. (1999) study, empirical evidence from other studies has suggested greater vulnerability to neurocognitive effects in children less than five years of age at diagnosis. For instance, Copeland and colleagues (1996) found a significant negative correlation between age at diagnosis and performance on perceptual-motor tasks, such as the Beery Visual-Motor Integration Test and the Block Design subtest of the Wechsler Intelligence Scale for Children (WISC). That is, the younger the child was at the time of diagnosis, the poorer the child's performance on these nonverbal neurocognitive measures. Another recent study found that children who were younger at diagnosis were significantly more likely to perform more poorly on the WISC Vocabulary and Digit Span subtests (Waber et al., 2001). Although both the Copeland and Waber studies found a relation between age and neurocognitive effects, it is interesting to note the difference in which tasks and domains were affected.

A second risk factor that has been identified in the literature is gender. Although girls generally have a better prognosis than boys in terms of risk for relapse, they are generally thought to be more vulnerable to long-term neurocognitive treatment effects. One study found that girls treated with high-dose methotrexate scored approximately 9.3 IQ points lower than boys receiving the same treatment (Waber et al. 1995). In another

study, males scored an average of 15 Full-Scale IQ points higher than females and also scored significantly higher for both Verbal and Performance IQ, as well as long-term verbal memory and visual motor integration (Iuvone et al. 2002). The reason for this significant gender difference remains unclear, however, one plausible explanation offered by Bleyer and colleagues (1990) is that brain development occurs at a faster rate in girls than boys during childhood, making girls' brains even more vulnerable to CNS prophylactic treatments designed to target rapidly growing leukemic cells in the brain and spinal cord. Therefore, it is possible that there is an age X gender interaction whereby young age at diagnosis is a factor for experiencing deficits in neurocognitive functioning for girls treated for ALL but not for boys. Unfortunately, research on the potential causes of gender differences in neurocognitive treatment sequelae is lacking.

Finally, it appears that length of time since the termination of ALL treatment is associated with greater likelihood of survivors exhibiting neurocognitive sequelae. Research has found that children's performance on neurocognitive measures decreases over time. Few longitudinal studies have assessed children at multiple time points throughout treatment and for several years following the end of treatment, but those that have demonstrate a rather steady decline in functioning (e.g., Rubenstein, Varni & Katz, 1990). It is likely that this phenomenon reflects a disruption in normative brain and neurocognitive development rather than an actual decline in ability (e.g., Armstrong, Blumberg, & Toledano, 1999).

Coping with Stress

If executive functions are adversely affected in pediatric cancer survivors, one of the processes that may be disrupted is the ability to regulate emotions and cope with stress. In the present study, coping is conceptualized according to the multidimensional model of responses to stress developed by Compas and colleagues (Connor-Smith et al., 2000). The model encompasses of both voluntary and involuntary responses to stress. However, this study will focus only on voluntary responses, which are thought to be self-regulatory efforts that depend on intact higher order executive function. Coping is defined as "conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (Compas et al., 2001). This model distinguishes coping on a dimension of engagement with or disengagement from a stressors or one's reactions to the stressors. Engagement responses are further differentiated into primary control strategies and secondary control strategies, depending on the goal they aim to serve. This model has been validated in several independent samples of children and adolescents (e.g., Calvita & Connor-Smith, 2004; Compas et al., 2006; Connor-Smith et al., 2000; Wadsworth et al., 2004).

Primary control coping responses are directed toward changing the stressor itself or one's emotional response to the stressor, including problem solving (e.g., I try to think of different ways to change the problem or fix the situation), emotional modulation (e.g., I keep my feelings under control when I have to, then let them out when they won't make things worse), and emotional expression (e.g., I let someone or something know how I feel). Secondary control coping responses are directed toward adapting to the stressor or ensuing emotional responses, including positive thinking (e.g., I tell myself that

everything will be all right), cognitive restructuring (I think about the things that I am learning from the situation, or something good that will come from it), acceptance (e.g., I realize that I just have to live with things the way they are), and distraction (e.g., I keep my mind off the problem by exercising, playing video games, seeing a friend, doing a hobby, and/or watching TV). Both primary and secondary control coping responses have been associated with lower levels of emotional and behavioral problems in children and adolescents (e.g., Compas, Boyer et al., 2006; Connor-Smith et al., 2000; Thomsen et al., 2002; Wadsworth & Compas, 2002).

Disengagement coping responses are characterized by attempts to orient oneself away from the stressor or one's emotional responses to the stressor. These include avoidance (e.g., I try to stay away from people and things that make me feel upset or remind me of the problem), denial (e.g., I say to myself "This isn't real), and wishful thinking (e.g., I deal with the problem by wishing it would just go away, that everything would work itself out). In contrast with the engagement coping responses described above, which appear to be adaptive, disengagement coping responses have been associated with higher levels of emotional and behavioral problems (e.g., Connor-Smith et al., 2000).

Executive Function and Coping Responses

Coping responses are one type of a broader category of behaviors that are aimed at regulating emotion, cognition, behavior, and physiology (Compas et al., 2001). As such, coping can be viewed as a type of executive function (Compas, 2006). A recent study examined the role of one domain of executive functioning, executive inhibition, in

the coping responses of children with attention and externalizing problems (Copeland & Compas, 2007). Executive inhibition refers to the ability to suppress dominant prepotent or previously reinforced responses to stimuli (Roberts & Pennington, 1996). In this study, inhibitory control was measured using three standardized tests of the ability to delay and inhibit behavioral responses (a go-no go task, a Stroop color naming task, and a delay of gratification task). Copeland and Compas (2007) found that engagement coping strategies, including primary control and secondary control coping, were associated with greater inhibitory control, while disengagement coping was associated with poorer inhibitory control. Further, primary control coping responses mediated the association between inhibitory control and externalizing behavior problems. That is, poor inhibitory control was related to more externalizing problems in part because of deficits in the use of primary control coping strategies. This study provided initial evidence that executive inhibition is important in the development and execution of effective coping strategies. The proposed study seeks to build on the findings from this study by examining multiple domains of executive function in addition to inhibition.

Executive Function, Coping, and Emotion Regulation in ALL Survivors

Several studies have found that children with cancer report lower levels of emotional distress when compared to normative data (Elkin, Phipps, Mulhern, & Fairclough, 1997; Phipps & Srivastava, 1997) and healthy control samples (Phipps & Srivastava, 1997; Phipps & Steele, 2002). Most of the patients sampled in these studies were still receiving treatment for ALL and therefore late effects were not assessed. However, a CCSS study published by Recklitis and colleagues (2006) in which a

heterogeneous cohort of adult childhood cancer survivors, including those treated for ALL, were administered the Brief Symptom Inventory-18, found that when compared to community participants or adult cancer patients, childhood cancer survivors reported significantly less psychological distress. In contrast, another CCSS study (Hudson et al., 2003) examining various quality of life domains in adult survivors of childhood cancer, including ALL, found that survivors reported significantly more symptoms of psychopathology compared to their healthy adult siblings. While the findings regarding late emotional and behavioral sequelae of childhood ALL treatment are mixed, there is good reason to believe that childhood ALL survivors are at risk for psychological problems.

Given the important role that executive function may play in the development and implementation of coping strategies and the link between maladaptive patterns of coping and emotional and behavioral problems, it is possible that the treatment-related declines in executive function described above lead to difficulties in generating effective coping strategies, which in turn leads to emotional and behavioral problems in survivors of childhood ALL. The focus up until now in the field has mainly been on the implications of neurocognitive effects for academic achievement and work performance. However, there may well be an additional implication on the regulation of emotion and the ability to effectively cope with stress in childhood ALL survivors.

Rationale for the Current Study and Hypotheses

The current study examined executive function, coping, and emotional and behavioral outcomes in children and adolescents who have completed treatment for ALL

and a matched control sample of healthy children. A total of seven hypotheses were tested. The first three hypotheses focus on between-group comparisons in order to determine the extent to which childhood ALL survivors evidence impairment or problems compared to a healthy matched control group on the abovementioned variables: 1) As shown in previous studies, compared to healthy controls, childhood ALL survivors will exhibit poorer performance on several domains of executive function, including working memory, mental flexibility, and behavioral inhibition. 2) Childhood ALL survivors will demonstrate patterns of less adaptive coping compared to healthy controls. That is, ALL survivors are expected to employ significantly more disengagement strategies and fewer primary and secondary control coping strategies. (3) Compared to the healthy control sample, childhood ALL survivors will evidence higher levels of emotional and behavioral problems.

The last four hypotheses focus on within-group analyses of the relations among the executive function, coping, and emotional variables among the survivors of ALL and healthy controls. While these relations may be significant in both groups, it is expected that they will be stronger in the ALL group due to the predicted treatment-related impairment: (4) The use of primary and secondary control coping strategies will be positively correlated with performance on measures of executive function, whereas the use of disengagement coping will be negatively correlated with performance on executive function measures. (5) Levels of emotional and behavioral problems will be negatively correlated with performance on measures of executive function. (6) Levels of emotional and behavioral problems will be negatively correlated with the use of primary and secondary control coping strategies, whereas levels of internalizing and externalizing

behavior problems will be positively correlated with the use of disengagement coping strategies. (7) Coping strategies will mediate the relation between executive function and emotional and behavioral problems.

CHAPTER II

METHODS

Participants

Participants included 30 children and adolescents between 10 and 20 years of age who completed treatment for ALL and 30 healthy controls matched on age, sex, and when possible SES. This age range was selected because research suggests that late childhood and adolescence is an important period of continued myelination of the prefrontal cortex and development of executive functions and therefore may represent an age at which children are especially vulnerable to the effects of intrathecal cancer treatments (e.g., Klinberg et al. 1999). Children currently within the specified age range who were treated for ALL at Vanderbilt Children's Hospital were required to meet the following criteria to be eligible for the study: (1) completed treatment for a diagnosis of standard- or high-risk ALL; (2) did not receive cranial irradiation and/or bone marrow transplantation; (3) were in continuous first remission (i.e., no history of disease relapse). ALL survivors were excluded if they had a history of CNS pathology requiring radiation or surgery, a history of other cancer diagnoses or major medical illnesses with known neurocognitive sequelae (e.g., meningitis), known premorbid neurodevelopmental or learning problems, or a history of very low birth weight (< 1500 grams), which is also associated with neurocognitive impairment.

In order to participate, healthy control participants were required to have working comprehension of the English language, have no history of cancer, major medical

illnesses, neurodevelopmental or learning disorders (including ADHD), and normal birth weight.

A total of 63 children and adolescents treated for ALL with chemotherapy only and currently within the study age range were identified, 27 of whom could not be contacted as they had moved since their last follow-up appointment at Vanderbilt Children's Hospital and did not have updated contact information. One ALL survivor relapsed prior to recruitment and was therefore ineligible to participate. Another ALL survivor had a history of bacterial meningitis, which, like ALL, is associated with impaired executive function (e.g., Schmidt et al., 2006), and was therefore also deemed ineligible to participate in the current study. Four additional ALL survivors declined participation. Therefore, of the 34 eligible ALL survivors we were able to contact, 30 (88%) were successfully recruited for and completed the study.

Demographics of the ALL and healthy control groups are provided in Table 1. There was no difference between the groups with regard to age at time of testing ($t = .12$, p = n.s.). With regard to level of parental education, 60% of the primary caregivers in the ALL group and 93.4% of those in the control group had at least some college education, a statistically significant difference ($t = -4.03$, $p < .01$). However, the groups did not differ on household income ($\chi = 1.15$, p = n.s.).

The mean age at time of diagnosis for the ALL group was 5.65 years (range = 1 to 14.30 years) and ALL participants had been off treatment an average of 6.05 years (range = 3 months to 13.96 years). At the time of the study assessment, the mean age of the ALL participants was 14.4 years and the mean age of the healthy control participants was 14.31 years. Eighty-six percent of the ALL group identified as White, 7% as African

American, and 7% as Biracial. Ninety percent of the control group identified as White, with the remaining 10% identifying as Biracial. Fifty percent of each group was female.

Table 1

Demographics of ALL Survivors and Healthy Controls

Variables	ALL	Healthy Control
Sex		
Female	15 (50%)	15 (50%)
Male	15 (50%)	15 (50%)
Race/ethnicity (n, %)		
White/Caucasian	26 (86.70%)	27 (90.00%)
Black/African American	3 (10.00%)	1 (3.33%)
Latino	0	1 (3.33%)
Biracial	1 (3.30%)	1 (3.33%)
Main Caregiver (n, %)		
Biological Mother	24 (80.00%)	26 (86.60%)
Biological Father	4 (13.30%)	2 (6.70%)
Stepmother	1 (3.30%)	2 (6.70%)
Grandmother	1 (3.30%)	0
Parent Education (n, %)		
High School Graduate	21 (70.00%)	7 (23.40%)
College Degree	9 (30.00%)	23 (76.60%)
Household Income		
<$50,000/year	9 (30.00%)	11 (36.60%)
≥$50,000/year	21 (70.00%)	19 (63.40%)
Age at Testing (in years)		
Mean (SD)	14.49 (2.88)	14.31 (2.76)
Range	10.11 – 20.78	10.27 – 19.64
Age at ALL Diagnosis (in years)		
Mean (SD)	5.65 (3.07)	NA
Range	1.00 – 14.30	NA
Time Since Treatment Ended (in years)		
Mean (SD)	6.05 (3.35)	NA
Range	.25 – 13.96	NA

Measures

Demographic and Medical Data. A brief intake interview was conducted with parents or caregivers in order to obtain basic demographic data, including relevant information regarding the child's developmental, medical, and academic history. The Demographic Intake Form, which was adapted from a longitudinal multicenter study conducted by the Children's Oncology Group (COG ALTE02C2), was used to record the abovementioned information (see Appendix A). In addition, diagnostic and treatment information for children previously treated for ALL was obtained by reviewing medical records.

Neurocognitive Functioning. The Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) or The Wechsler Adult Intelligence Scale—Third Edition (WAIS-III), depending on the age of the participant, was administered to measure overall cognitive ability, working memory, and processing speed**.** Although the Working Memory Index (WMI), which is comprised of the Digit Span and Letter-Number Sequencing subtests, was the index of most interest to the study as it was one of the main behavioral executive function measures, the ALL and healthy control groups were also compared on Full Scale IQ (FSIQ) and the Processing Speed Index (PSI), and these variables were also examined as potential covariates. The Wechsler intelligence scales demonstrate good internal consistency (r = .97) and tests-retest reliability (r = .93), and convergent and discriminant validity has been established.

In addition to WMI of the WISC-IV and WAIS-III, three other subdomains of executive function were also measured directly using the Delis-Kaplan Executive Function System (D-KEFS), a comprehensive battery of tests that assesses verbal and

nonverbal executive functions in individuals ages 8 to 89. The D-KEFS was standardized on 1,700 individuals children and adults selected to match several demographic characteristics of the U.S. population (Delis, Kaplan, & Kramer, 2001). Each of the D-KEFS tests can be used as a stand-alone instrument that can be administered individually or in combination with other D-KEFS tests. In addition to higher level executive functions, all of the D-KEFS tests also assess component functions (i.e., fundamental cognitive skills on which executive functions depend) in order to better determine reasons for poor performance. The D-KEFS tests yield age-corrected scaled achievement and process scores that have a mean of 10 and a standard deviation of 3.

Three D-KEFS tests were administered for the current study: the Color-Word Interference Test, the Sorting Test, and the Tower Test. First, the D-KEFS Color-Word Interference Test measures two domains of executive function: behavioral inhibition and cognitive flexibility. This test includes two conditions assessing the component functions of basic naming of color patches and basic reading of words denoting colors, which presumably are skills required to perform the higher-level tasks presented in the last two conditions. The third condition is the traditional Stroop interference task, in which the examinee is required to inhibit the prepotent response of reading the words denoting colors in order to name the dissonant ink colors in which the words are printed. Finally, the fourth condition requires the examinee to switch back and forth between naming the dissonant ink colors and reading the conflicting words. Normative data are provided for completion times for each of the four conditions and contrast measures for determining for parceling scores on component function conditions from scores on higher-level tasks. For the current study, only scores for the third condition, the Stroop color-word

interference task that measures behavioral inhibition, were used in the statistical analyses, as it most directly measures this particular domain of executive function.

The D-KEFS Sorting Test measures verbal and nonverbal problem-solving, conceptual reasoning, and the initiation of problem-solving behavior. The test consists of two testing conditions: Free Sorting and Sort Recognition. For the first condition, examinees are presented with cards displaying perceptual features and printed words and are required to sort them into groups according to as many different concepts or rules they can think of. In the second condition, the examiner sorts the same sets of cards according to eight possible target sorts and asks the examinee to identify and describe the rules or concepts by which the cards were sorted. Normative data are provided for number of confirmed correct sorts and descriptions for the Free Sorting Condition and sort recognition descriptions for the second condition. Additionally, a combined description score is calculated across both conditions, as well as a contrast score in descriptions between the two conditions. For the current study, only the Free Sort description scores were included in the analyses because it measures the executive function domain of cognitive flexibility and set-shifting ability.

Finally, the D-KEFS Tower Test measures several domains of executive function, including spatial planning, rule learning, inhibition of impulsive responding, inhibition of perseverative responding, and establishing and maintaining an instructional set. The test requires the examinee to move up to five disks that vary in size on a board with three pegs in order to construct increasingly more complex "towers" in the fewest number of moves possible. In order to construct the target tower, the examinee must follow two rules: (1) only move one disk at a time and (2) never place a larger disk over a smaller

one. The Total Achievement score, which is based on the number of moves it took the participant to complete the towers, was used in the statistical analyses.

In addition to these direct behavioral measures, executive function was also assessed through parent report. Participants' primary caregivers completed the Brief Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000), a questionnaire that allows parents to rate their children on a list of 86 problem behaviors reflecting various domains of executive function over the past six months according to a three-point scale: N if the behavior is *n*ever a problem, S if the behavior is *s*ometimes a problems, O if the behavior is *o*ften a problem, scored as 1, 2, or 3, respectively. The BRIEF yields scale scores (raw scores and T scores) for eight different domains of executive function: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organizations of Materials, and Monitor. In addition, three broader index scores confirmed by factor analyses are generated (Gioia, Isquith, Retzlaff, & Espy, 2002). The Behavioral Regulation Index (BRI) is obtained by summing the scores for the Inhibit, Shift, and Emotional Control scales. The Metacognition Index (MI) is obtained by summing the scores for Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. Finally, the Global Executive Composite (GEC), which reflects the child's overall executive functioning across all of the domains measured, is obtained by summing the BRI and MI indexes. The BRIEF was standardized on 1,419 parents with demographic compositions representative of the 1999 US census. It has high internal consistency (alphas = .80-.98) and test-retest reliability (r = .82), and convergent validity has been established with other measures of executive function (Gioia et al., 2000). It should also be noted that for the current study, the BRIEF

was reverse scored to reflect more problems, which facilitated its interpretation and comparison with the other study measures in the statistical analyses.

For the purpose of this study, only the Working Memory, Inhibit, Shift, and Monitor subscales of the BRIEF were used, as they were deemed to most closely measure the executive functions behaviorally assessed with the WISC/WAIS WMI (BRIEF Working Memory), D-KEFS Color-Word (BRIEF Inhibit)—both are measures of behavioral inhibition, D-KEFS Sorting Test (BRIEF Shift)—both are measures of cognitive flexibility, and D-KEFS Tower (BRIEF Monitor)—both reflect the ability to self-monitor one's behavior.

Coping. The Responses to Stress Questionnaire (RSQ), both self- and parent-report versions, was administered to assess the coping responses of ALL and healthy control participants (Connor-Smith et al., 2000). It has been adapted to specifically target coping responses related to social stress, a domain in which both ALL survivors and controls are likely to have experienced a sufficient base rate of stressors to complete the measure. The RSQ measures both voluntary and involuntary responses to stress; however, the current study focuses solely on the three voluntary coping domains: Primary Control coping (problem solving, emotional modulation, emotional expression), Secondary Control coping (acceptance, cognitive restructuring, positive thinking, distraction), and Disengagement coping (avoidance, denial, wishful thinking). With regard to its reliability and validity, the RSQ has been shown to have good test-retest reliability (alphas ranged from .69 to .81) and internal consistency (alphas ranged from .67 to .92), and convergent and discriminant validity has been established.

Emotional and Behavioral Problems. The Child Behavior Checklist (CBCL; Achenbach, 1991) was administered to all parents or caregivers in order to determine their perceptions of the children's emotional and behavioral functioning and competencies over the past six months. Similarly, the Youth Self-Report (YSR; Achenbach, 1991) was administered to all children participating in the study in order to determine their perceptions of their own functioning. Both the CBCL and the YSR require respondents to report the frequency of 112 problem behaviors or symptoms on a three-point scale: 0 = Not True; 1 = Somewhat or Sometimes True; 2 = Very True or Often True. Both questionnaires yield raw and T scores indicating children's level of overall internalizing and externalizing problems and more specific syndromes, including Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. The Achenbach System of Empirically-Based Assessment (ASEBA), which includes the CBCL and YSR, demonstrates strong test-retest reliability (.75-.95), as well as good convergent and discriminant validity. For the purpose of this study, only internalizing and externalizing problems will be included in the analyses.

Procedure

The parents or caregivers of ALL survivors were sent a letter from a physician who was not involved in the child's clinical care inviting them to participate in the proposed research study (see Appendix B). The physician then placed a follow-up call to the family approximately one week after the letter was sent to answer any questions about the study and to gauge the family's interested in participating. If families expressed

interest, an appointment was scheduled for them to come to the Pediatric Hematology/ Oncology clinic for study assessment.

Upon arriving for the session, informed consent and assent was obtained from participants and parents. After answering any questions, the examiner asked interested parents and patients to sign the Consent and Assent Forms, respectively (see Appendix C and D). At this time, the examiner also asked ALL participants and parents to generate a list of peers who were of the same age and sex in order to identify healthy controls for the study. ALL participants were shown copies of three different versions of a letter that could be sent to potential healthy controls inviting them to participate in the study (see Appendix E). The first letter would be sent to peer nominees if the ALL participant wanted to be personally identified as a participant in this study and to disclose his or her status as a leukemia survivor. The second letter would be sent if the ALL participant chose to be identified but did not wish to reveal that he or she was treated for leukemia. Finally, the third letter would be sent if the ALL participant chose to remain completely anonymous. ALL participants and their parents were given the opportunity to decline this method of identifying controls. Only five healthy controls were identified by this method, as the remaining ALL participants declined to nominate peers, usually because they assumed none of their friends would be interested or have time to participate. Therefore, healthy controls were also recruited through Vanderbilt University Medical Center Clinical Trials Office. Specifically, a mass email was sent to staff and faculty at the Vanderbilt Medical Center advertising for a study examining neurocognitive development in children and adolescence (see Appendix F). The email distribution list includes all staff and faculty who have email addresses, ranging from clerical staff to

medical professional staff and faculty. Interested individuals who responded to the email were administered a screening interview to determine whether the child met criteria and also whether the child was an age and sex match to an ALL participant who already enrolled in the study. Excluding the identification of peers for potential recruitment, the procedure for obtaining consent and assent and data collection was the same for healthy controls participating in this study (see Appendices G and H for healthy control consent and assent forms).

Next, the examiner conducted a brief demographic intake interview with the parent and asked the parent to complete the CBCL, BRIEF, and the parent-report version of the RSQ in a separate room. The examiner then administered the YSR and the self-report version of the RSQ to the child. Once they completed the questionnaires, children were then administered the WISC-IV or WAIS-III, depending on the participant's age, and the D-KEFS tests mentioned above. The average appointment lasted approximately three hours. Following testing, completed questionnaires were collected from the parent, parents and children were debriefed, and each received an honorarium of $25, and an additional $10 to compensate for any travel costs.

Statistical Analyses

Means and standard deviations were calculated for neurocognitive, coping, and emotional and behavioral outcomes, and between-group differences were examined for each of these variables using independent samples t-tests. In addition, effect sizes (Hedges *g*s) were calculated to determine the magnitude of effects comparing the ALL group to the healthy control group and both groups to normative data. Hedges *g*

represents the number of standard deviations the ALL group means on a given neurocognitive test differ from the mean of the normative or comparison group. Positive effect sizes indicate that the ALL group performed better than the normative or control sample. Conversely, negative values indicate that the ALL group performed more poorly. According to Cohen (1988), effect sizes less than .2 indicate negligible effects, those between .2 and .5 indicate small effects, those between .5 and .8 indicate medium effects, and those greater than .8 are considered large effects.

Pearson product-moment correlation coefficients for relations between executive function, coping, and emotional and behavioral outcome variables were conducted separately for the self- and parent-reported data in each group.

Hierarchical linear multiple regression analyses were conducted to predict internalizing and externalizing behavior problems from each executive function and coping factor. More specifically, coping was tested as a mediator of the relation between executive function and emotional problems following the methodology discussed by Baron and Kenney (1986). In accordance with this method, three criteria must be met in order to test for mediation: (1) executive function measures significantly correlated with internalizing and externalizing behavior problems; (2) coping variables significantly correlated with internalizing and externalizing behavior problems; (3) executive function measures significantly correlated the coping variables. When all three criteria were met for a set of independent and dependent variables, a regression equation was conducted entering the executive function variable in the first step and entering the coping variable in the second step in order to test for mediation. Evidence for a fully mediated model occurs when executive function significantly predicts emotional problems in the first step

but is no longer significant once the coping variable is added in the second step. Evidence for a partially mediated model occurs when both the executive function and coping variables remain significant predictors of emotional problems in the second step. When either form of mediation was demonstrated through these regression analyses, a Sobel test was performed in order to test the indirect effect of the independent variable on the dependent variable through the mediator using the following equation (Sobel, 1982):

$$z = \frac{ab}{\sqrt{b^2 s_a^2 + a^2 s_b^2 + s_a^2 s_b^2}}$$

In Sobel's formula, the path from the independent variable (executive function) to the mediator (coping) is denoted as "a" and the standard error as "s_a". The path from the mediator (coping) to the dependent variable (emotional problem) is denoted by "b" and its standard error is "s_b".

Statistical Power

Given the results from a recently published meta-analysis, which demonstrated mostly small to medium effect sizes when comparing ALL and control groups on various neurocognitive functions, similar effects were expected to be found in the current study (Campbell et al., in press). However, power analyses indicated that with the current sample of 30 participants in each group, the power to detect small effects ($d \geq .2$) was .19, medium effects ($d \geq .5$) was .61, and large effects ($d \geq .8$) was .92. In order to compensate for lower power, effect sizes were conducted and presented in this paper to better display between-group differences, as it was expected that some between-group results would not be statistically significant. With regard to within-group relations

among variables, the power to detect correlations of .40 or greater at the $p < .05$ level of significance was adequate (.72).

CHAPTER III

RESULTS

Descriptive Statistics

Means and standard deviations for executive function, coping, and emotional and behavioral problems are reported in Table 2. With regard to WISC/WAIS scores, FSIQ for the ALL group fell within the Average range and were in the High Average range for the healthy control group. WMI and PSI scores fell within the Average range for both the ALL and healthy control groups. Likewise, all D-KEFS and BRIEF scores for both groups fell within the average range (see Table 2 for mean scores and standard deviations).

Demographic, medical, and cognitive variables were examined separately for each group to determine if they were significantly correlated with the dependent variables (internalizing and externalizing behavior problems) and should therefore be controlled for in the regression analyses. Sex and age at the time of the evaluation were examined in both groups, and age at time of diagnosis and number of years since treatment were also examined in the ALL group. None of these variables were significantly correlated with CBCL and YSR internalizing or externalizing symptoms in either group.

Because processing speed was expected to be related to the key variables, as impairment of this neurocognitive domain is common in ALL survivors, correlational analyses were also performed between WISC/WAIS FSIQ, WISC/WAIS PSI and the dependent variables, internalizing and externalizing behavior problems. Again, no

significant correlations were found between FSIQ or PSI and the behavioral outcome variables for either group.

Table 2

Mean Scaled Scores and Standard Deviations for FSIQ and the Executive Function Variables

Overall Cognitive Ability and Executive Function	**ALL Group Mean (SD)**	**Healthy Control Group Mean (SD)**
WISC-IV/WAIS-III FSIQ	100.89 (15.37)	113.33 (11.16)
WISC-IV/WAIS-III PSI	93.28 (14.68)	102.96 (15.30)
WISC-IV/WAIS-III WMI	97.27 (16.32)	106.38 (13.01)
D-KEFS Color-Word Interference	10.57 (2.08)	10.40 (2.27)
D-KEFS Sorting Test	10.60 (3.04)	11.83 (2.07)
D-KEFS Tower Test	10.34 (2.27)	10.57 (2.45)
BRIEF Working Memory	51.75 (13.37)	46.81 (7.82)
BRIEF Inhibit	47.82 (13.00)	46.74 (6.30)
BRIEF Shift	52.14 (18.32)	47.81 (8.29)
BRIEF Monitor	51.18 (15.62)	48.30 (9.37)
RSQ scales	**Self / Parent**	**Self / Parent**
Primary Control Engagement	.20 (.04) / .22 (.05)	.20 (.04) / .23 (.04)
Secondary Control Engagement	.26 (.05) / .25 (.05)	.27 (.04) / .26 (.05)
Disengagement	.14 (.03) / .15 (.03)	.15 (.03) / .15 (.03)
Emotional/Behavioral Outcomes	**YSR/CBCL**	**YSR/CBCL**
Internalizing Problems	52.30 (10.29) / 51.39 (12.49)	51.63 (7.80) / 53.31 (9.79)
Externalizing Problems	49.60 (9.15) / 50.39 (9.85)	51.73 (7.33) / 50.14 (8.79)

Note: Higher scores on the BRIEF indicate poorer performance

Cross-informant correlations

Cross-informant (i.e., parents and children) analyses were conducted by performing Pearson product-moment correlations among the self-reported and parent-reported coping and emotional problem variables independently for each group.

ALL Group. Self-reported primary control coping was not significantly correlated with parent-reported primary control coping or CBCL internalizing and externalizing problems, nor was it correlated with YSR internalizing or externalizing problems. Self-reported secondary control coping was significantly and negatively correlated with both CBCL and YSR internalizing and externalizing problems. It was not correlated with parent-reported secondary control coping but was positively correlated with parent-reported primary control coping. Self-reported disengagement coping was significantly and negatively correlated with parent-reported primary control coping but was not significantly correlated with parent-reported disengagement coping or CBCL and YSR internalizing and externalizing problems.

Parent-reported primary control coping was significantly and negatively correlated with CBCL internalizing and externalizing problems but not with the YSR. The correlation between parent-reported secondary control coping and YSR externalizing problems approached significance. Secondary control coping was not significantly correlated with YSR internalizing problems but did negatively correlated with CBCL internalizing and externalizing problems. Finally, parent-reported disengagement coping significantly correlated only with CBCL internalizing problems and approached significantly with externalizing problems.

Healthy Control Group. Self-reported primary control coping and disengagement coping were not significantly correlated with any of the parent-reported coping variables, nor were they correlated with CBCL or YSR internalizing and externalizing problems. However, self-reported secondary control coping was negatively correlated with parent-reported disengagement coping and YSR internalizing problems.

The correlation between parent-reported primary control coping and CBCL internalizing approached significance. It was not correlated with either of the YSR variables. Parent-reported secondary control coping was not correlated with CBCL or YSR variables. Finally, parent-reported disengagement coping was positively correlated with YSR internalizing problems only.

Hypotheses

The rest of the results section is organized in correspondence with each of the seven hypothesis outlined above.

Hypothesis 1. First, it was predicted that compared to healthy controls, childhood ALL survivors would exhibit poorer performance on several domains of executive function, including working memory, mental flexibility, and behavioral inhibition. Comparisons between the ALL and healthy control groups were made using independent samples t tests. With regard to the executive function measures, significant differences were found on the WISC-IV/WAIS III WMI ($t = -2.15$, $p < .05$), while the BRIEF Working Memory Scale and the D-KEFS Sorting Test approached significance ($t = -1.89$, $p = .06$; $t = -1.86$, $p = .07$, respectively. In addition, the groups significantly differed on WISC/WAIS FSIQ ($t = -3.37$, $p < .01$) and WISC/WAIS PSI ($t = -2.50$, $p < .05$). These

group differences were in the predicted direction, with the ALL group evincing poorer performance than the healthy control group. No significant between-group differences were detected for any of the other executive function measures, nor the coping or emotional outcome measures.

Because the two groups differed significantly with regard to parent education, with more healthy control parents having more college education that ALL parents ($t = -4.03$, $p < .01$), and parent education is a significant predictor of intelligence in children, analyses of covariance were also run comparing the groups on FSIQ, PSI, and the executive function measures with parent education entered as a covariate. The following between-group differences still remained significant or approached significance even after accounting for parent education: WISC/WAIS FSIQ [$F (2, 55) = 6.21$, $p < .05$]; WISC/WAIS WMI [$F (2, 55) = 3.07$, $p = .07$); BRIEF Working Memory [$F (2, 55) = 3.09$, $p = .07$). The between-group differences between the D-KEFS Sorting Test and WISC/WAIS PSI no longer approached significance. It should be noted, however, that parent education did not account for a statistically significant amount of variance in any of these analyses.

In addition to t-tests, effect sizes (Hedges *g*s) were calculated to determine the magnitude of effects comparing the ALL group to the healthy control group and also comparing both groups to normative samples (see Table 3). Hedges *g* represents the number of standard deviations the ALL group means on a given neurocognitive test differ from the mean of the normative or comparison group. Positive effect sizes indicate that the ALL group performed better than the normative or control sample. Conversely, negative values indicate that the ALL group performed more poorly.

Table 3

Effect sizes (Hedge's gs) Comparing ALL Sample to Normative Data and a Matched Healthy Control Sample

Neurocognitive Measure	ALL vs Normative Data	Healthy Control vs Normative Data	ALL vs Healthy Control
WISC/WAIS FSIQ	+.06	+1.02	-.94
WISC/WAIS PSI	-.45	+.20	-.62
WISC/WAIS WMI	-.17	+.46	-.62
D-KEFS Color-Word Inhibit	+.22	+.15	-.23
D-KEFS Sorting Test	+.20	+.72	-.48
D-KEFS Tower Test	+.13	+.21	-.10
BRIEF Working Memory	-.15	+.36	-.53
BRIEF Inhibit	+.19	+.40	-.06
BRIEF Shift	-.15	+.24	-.30
BRIEF Monitor	-.01	+.18	-.22

Note: Negative signs indicate that the ALL group performed more poorly on the measure compared with the normative or comparison group; Positive signs indicate that the groups performed better than the control group or that the ALL group performed better than the healthy control group.

All effect sizes comparing the ALL group to the control group on the executive function measures were in the negative (expected) direction indicating poorer functioning. The effects comparing the groups on executive function measures ranged from negligible to medium (g = -.06 to -.62; see Table 3). Medium effects were found for WISC-IV/WAIS-III WMI (g = -.62) and BRIEF Working Memory (g = -.53). Small effects were found for the D-KEFS Sorting Test (*g* = -.48), D-KEFS Color-Word Inhibition (g = -.23), BRIEF Shift (g = -.30), and BRIEF Monitor (g = -.22). In addition, a large effect was found for WISC/WAIS FSIQ (g = -.94), and a medium effect was found for WISC/WAIS PSI (g = -.62).

When the ALL group was compared with normative data on the WISC/WAIS and D-KEFS, only one small negative effect was found: WISC/WAIS PSI (g = -.45). All other effects were either negligible or small positive effects, which were unexpected (see Table 3). When comparing the healthy control group to normative data, all effects were in the positive direction, ranging from negligible to large (+.15 to +1.02), with FSIQ being the largest.

Hypothesis 2. The second hypothesis predicted that childhood ALL survivors would demonstrate patterns of less adaptive coping compared to healthy controls. That is, ALL survivors were expected to employ significantly more disengagement strategies and fewer primary and secondary control coping strategies. No significant differences were found between the two groups with regard to self- or parent-reported coping strategies. Both raw scores (the number of coping responses endorsed for each domain of coping) and proportion scores (raw scores divided by the overall number of coping responses endorsed) were examined.

Effect sizes (Hedges' gs) were also computed to compare the ALL and healthy control groups with regard to coping strategies. Small but non-significant effects were found for both self-reported secondary control coping (g = -.36) and parent-reported secondary control coping (g = -.20), with ALL patients and their parents consistently endorsing a lower proportion of secondary control strategies than did healthy control participants and their parents. Effects for primary control coping and disengagement coping were negligible.

Hypothesis 3. The third hypothesis predicted that compared to the healthy control sample, childhood ALL survivors will evidence higher levels of internalizing problems. However, no significant between-group differences were found with regard to the CBCL or YSR variables. Also, contrary to the hypothesis, the effect size for the CBCL Internalizing Scale, although non-significant, was small and in the positive direction (g = +.23), indicating that healthy control parents endorsed greater internalizing symptoms than did the ALL parents. On the other hand, the YSR Internalizing effect size was negligible and in the negative direction (g = -.09). The Externalizing scales on both the CBCL and YSR were negligible. When the CBCL syndrome scales were examined, small but non-significant negative effects were found for the Social Problems (g = -.45), Attention Problems (g = -.41), and Rule-Breaking (g = -.22) scales, indicating that ALL parents endorsed more symptoms on these scales than did healthy control parents. Surprisingly, a small (but non-significant) positive effect was found for the Somatic Problems scale (g = +.30), showing that healthy control parents reported greater symptoms in their children than parents of ALL survivors.

With regard to the YSR syndrome scales, small non-significant negative effects were found for the Anxious/Depressed (g = -.24) and Somatic Problems (g = -.36) scales, indicating that ALL participants endorsed more symptoms on these scales than did healthy control participants. Small (but on-significant) positive effects were found for

the following YSR syndrome scales: Withdrawn/Depressed (g = +.21), Social Problems (g = +.28), and Aggressive Problems (g = +.36), indicating that healthy control participants endorsed more symptoms on these scales than did ALL participants.

Hypothesis 4. The fourth hypothesis predicted that the use of primary and secondary control coping strategies would be positively correlated with performance on measures of executive function, whereas the use of disengagement coping would be negatively correlated with performance on executive function measures. These correlations were expected to be stronger for the ALL group than the healthy control group.

ALL Group

All correlations among the executive function and coping measures for the ALL group that reached or approached statistical significance were in the expected directions. First, correlations among the various executive function measures and self-reported coping variables were examined (See Table 4). Consistent with the hypothesis, self-reported secondary control coping was positively correlated with BRIEF Working Memory (r = .55, p < .01), BRIEF Shift (r = .38, p < .05), and BRIEF Monitor (r = .52, p < .01). The correlation between BRIEF Inhibit and self-reported secondary control coping approached significance (r = .32, p = .07). Also in accordance with the hypothesis, self-reported disengagement coping was negatively correlated with the WISC/WAIS WMI (r = -.44, p < .05), D-KEFS Tower Test (r = -.42, p < .05), BRIEF Working Memory (r = -.47, p < .05), and BRIEF Monitor (r = -.41, p < .05). The correlation between BRIEF Inhibit and self-reported disengagement coping approached

significance (r = -.35, p = .06). None of the correlations among the executive function measures and self-reported primary control coping were significant.

Next, the correlations among the executive function measures and parent-reported coping variables were examined (See Table 5). As expected, parent-reported primary control coping was positively correlated with WAIS/WISC WMI (r = .43, p < .05), D-KEFS Sorting Test (r = .52, p < .01), BRIEF Working Memory (r = .69, p < .01), BRIEF Shift (r = .54, p < .01), BRIEF Inhibit (r = .66, p < .01), and BRIEF Monitor (r = .61, p < .01). Also consistent with the hypothesis, parent-reported secondary control coping was positively correlated with BRIEF Working Memory (r = .54, p < .01), BRIEF Shift (r = .45, p < .05), and BRIEF Monitor (r = .49, p < .01). Also as predicted, parent-reported disengagement coping was negatively correlated with BRIEF Working Memory (r = -.50, p < .01), BRIEF Inhibit (r = -.52, p < .01), and BRIEF Monitor (r = -.47, p < .05). The negative correlations between parent-reported disengagement coping and WAIS/WISC WMI and BRIEF Shift approached significance (r = -.36, p = .06 for both).

Healthy Control Group

No significant correlations were found among the executive function and self-reported coping variables for the healthy control group (See Table 4). However, several significant correlations, all in the expected directions, were found for parent-reported coping variables (See Table 5). Parent-reported primary control coping was positively correlated with WISC/WAIS WMI (r = .41, p < .05) and BRIEF Monitor (r = .38, p < .05). In addition, the correlation between parent-reported primary control coping and BRIEF Shift approached significance (r = .34, p = .07). Also, a negative correlation

between parent-reported disengagement coping and BRIEF Inhibit approached significance ($r = -.33$, $p = .08$).

Table 4

Correlations Among Executive Function, Self-Reported Coping, and Self-Reported Emotional and Behavioral Problems

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. WISC/WAIS WMI		-.20	-.08	**.43***	-.27	-.01	-.16	.35+	.06	.14	.26	-.26	-.17
2. D-KEFS Sorting	**.47****		**-.38***	-.10	.02	-.25	.21	.00	-.12	.14	.00	-.16	-.09
3. D-KEFS C-W Inhibit	.35+	-.21		.17	-.19	.17	-.32	.05	-.03	.02	.10	-.14	-.16
4. D-KEFS Tower	.32	.35+	**.51****		-.35+	-.10	-.16	.12	.25	.15	.04	-.28	-.24
5. BRIEF Working Memory	.25	**.49****	.04	.08		.28	**.41***	**.44***	.05	.06	-.14	-.01	-.24
6. BRIEF Shift	.20	**.46****	.00	.18	**.61****		.13	.34+	-.16	-.02	.07	.16	**-.38***
7. BRIEF Inhibit	**.41***	**.61****	.18	.18	**.74****	**.38***		.35+	.00	-.10	-.07	-.20	-.09
8. BRIEF Monitor	.26	**.54****	.02	.04	**.88****	**.70****	**.71****		.11	-.10	-.24	.06	.02
9. Primary Control Coping	.30	.20	.27	.22	.14	.18	.11	.22		-.01	**-.63****	-.26	-.33+
10. Secondary Control Coping	.09	.22	.12	.09	**.55****	**.38***	.32+	**.52****	.15		-.07	**-.42***	-.23
11. Disengagement Coping	**-.44***	-.30	.16	**-.42***	**-.47***	-.20	-.35+	**-.38***	**-.41***	**-.62****		-.01	.09
12. Internalizing Problems	.11	-.08	-.08	-.09	-.15	-.16	-.04	-.33+	.01	**-.64****	.20		**.54****
13. Externalizing Problems	-.35+	.11	**-.49****	-.26	-.21	-.09	.04	-.26	.04	**-.51****	.13	**.69****	

Note: Healthy control correlations are on the top right

BRIEF scales were reverse scored such that lower scores rather than higher scores indicate poorer functioning; + $p < .10$ (approaching significance), * $p <. 05$, ** $p < .01$

Table 5

Correlations Among Executive Function, Parent-Reported Coping, and Parent-Reported Emotional and Behavioral Problems

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. WISC/WAIS WMI		-.20	-.08	**.43***	-.27	-.01	-.16	.35+	**.41***	.18	.08	-.19	-.04
2. D-KEFS Sorting	**.47****		**-.38***	-.10	.02	-.25	.21	.00	-.01	.04	.07	.22	.27
3. D-KEFS C-W Inhibit	.35+	-.21		.17	-.19	.17	-.32	.05	.27	-.31	-.08	-.29	-.05
4. D-KEFS Tower	.32	.35+	**.51****		-.35+	-.10	-.16	.12	-.13	.11	-.04	-.08	.11
5. BRIEF Working Memory	.25	**.49****	.04	.08		.28	**.41***	**.44***	.31	.29	-.01	-.09	-.32
6. BRIEF Shift	.20	**.46****	.00	.18	**.61****		.13	.34+	.34+	-.10	-.27	**-.52****	**-.44***
7. BRIEF Inhibit	**.41***	**.61****	.18	.18	**.74****	**.38***		.35+	.08	.06	-.33+	.04	-.26
8. BRIEF Monitor	.26	**.54****	.02	.04	**.88****	**.70****	**.71****		**.38***	-.10	-.21	-.27	**-.54****
9. Primary Control Coping	**.43***	**.52****	.03	-.03	**.69****	**.54****	**.66****	**.61****		-.10	**-.66****	-.35+	-.18
10. Secondary Control Coping	.04	.27	.17	.27	**.54****	**.45***	.30	**.49****	**.48****		-.14	-.11	-.10
11. Disengagement Coping	-.36+	-.29	-.09	.20	**-.50****	-.36+	**-.52****	**-.47***	**-.72****	**-.63****		.32+	.09
12. Internalizing Problems	-.25	**-.42***	-.21	.15	**-.68****	**-.76****	**-.42***	**-.78****	**-.68****	**-.65****	**.66****		**.49****
13. Externalizing Problems	.01	**-.45***	-.14	.13	**-.80****	**-.66****	**-.62****	**-.76****	**-.60****	**-.66****	.34+	**.64****	

Note: Healthy control correlations are on the top right

BRIEF scales were reverse scored such that lower scores rather than higher scores indicate poorer functioning; + p < .10 (approaching significance), * p <. 05, ** p < .01

Between-Group Comparison of Correlations

It was predicted that associations among the executive function and coping variables would be stronger for the ALL group than for the control group. In order to compare correlations that were found to be significant or approaching significance among executive function and coping variables for the ALL and healthy control groups, Fisher's z-tests were computed using the following formula:

$$z = \frac{.5[\text{Ln}\,(1+r_1) - \text{Ln}\,(1-r_1)] - .5[\text{Ln}\,(1+r_2) - \text{Ln}\,(1-r_2)]}{(1/n_1 - 3) + (1/n_2)^{1/2}}$$

Only four sets of correlations were statistically significant or approached significance in the correlation matrices of both groups: WISC/WAIS WMI and Parent-Reported Primary Control Coping; BRIEF Monitor and Parent-Reported Primary Control Coping; BRIEF Shift and Parent-Reported Primary Control Coping; and BRIEF Inhibition and Parent-Reported Disengagement Coping. Contrary to the hypothesis, no between-groups differences were found regarding the strength of these relations ($z = .09$, $z = 1.13$, $z = .92$, and $z = -.86$, respectively).

However, it should also be noted that out of 128 possible correlations among the various executive function variables, self- and parent-reported coping variables, and self- and parent-reported emotional/ behavioral outcome variables for each group, 65 correlations (50.78%) were significant or approached significance for the ALL group, compared to only 17 (13.28%) for the healthy control group, and many of the differences between these correlations are statistically significant.

Hypothesis 5. The fifth hypothesis predicted that levels of internalizing and externalizing behavior problems would be negatively correlated with performance on measures of executive function.

ALL Group

All correlations among the executive function and emotional outcome measures for the ALL group that reached or approached statistical significance were in the expected directions. First, correlations among the various executive function measures and self-reported internalizing and externalizing behaviors were examined (See Table 4). Consistent with the hypothesis, a negative correlation between YSR internalizing behavior and BRIEF Monitor approached significance ($r = -.33$, $p = .08$). In addition, a significant negative correlation was found between YSR externalizing behavior and D-KEFS Color-Word Inhibition ($r = -.49$, $p < .01$). The correlation between YSR externalizing behavior and WISC/WAIS WMI also approached significance ($r = -.35$, $p = .06$).

Next, the correlations among the executive function measures and parent-reported emotional outcome measures were examined (See Table 5). As expected, CBCL internalizing behavior was negatively correlated with D-KEFS Sorting Test ($r = -.42$, $p < .05$), BRIEF Working Memory ($r = -68$, $p < .01$), BRIEF Shift ($r = -.76$, $p < .01$), BRIEF Inhibit ($r = -.42$, $p < .05$), and BRIEF Monitor ($r = -.78$, $p < .01$). Likewise, CBCL externalizing behavior was also negatively correlated with the same executive function measures: D-KEFS Sorting Test ($r = -.45$, $p < .05$), BRIEF Working Memory ($r = -.80$, p

< .01), BRIEF Shift (r = -.66, p < .01), BRIEF Inhibit (r = -.62, p < .01), and BRIEF Monitor (r = -.76, p < .01).

Healthy Control Group

Self-reported externalizing behavior problems on the YSR were negatively correlated with BRIEF Shift (r = -.38, p < .05; See Table 4). No other correlations among the self-reported emotional outcome variables and executive function measures were found for the healthy control group. With regard to parent-reported emotional variables, a significant negative correlation was detected between CBCL Internalizing Behavior and BRIEF Shift (r = -.52, p < .01; See Table 5). In addition, negative correlations were found between CBCL Externalizing Behavior and BRIEF Shift (r = -.44, p < .01) and BRIEF Monitory (r = -.54, p < .01).

Between-Group Comparison of Correlations

Again, it was predicted that associations among the executive function and emotional outcome variables would be stronger for the ALL group than for the control group. Between-group comparisons of significant correlations were conducted using Fisher's z-tests. Three sets of correlations were statistically significant or approached significance in both groups: BRIEF Shift and CBCL Internalizing Behavior, BRIEF Shift and CBCL Externalizing Behavior, and BRIEF Monitor and CBCL Externalizing Behavior. No between-groups differences were found regarding the strength of these relations (z = -1.54, z = -1.18, and z = -1.44, respectively).

Hypothesis 6. The sixth hypothesis predicted that levels of internalizing and externalizing behavior problems would be negatively correlated with the use of primary and secondary control coping strategies, whereas levels of internalizing and externalizing behavior problems would be positively correlated with the use of disengagement coping strategies.

ALL Group

All correlations among the coping and emotional variables that were statistically significant or approached significance were in the expected directions. Regarding self-reported coping and emotional outcomes, secondary control coping was negatively correlated with YSR internalizing problems ($r = -.64$, $p < .01$) and externalizing problems ($r = -.51$, $p < .01$; See Table 4). Self-reported primary control and disengagement coping were not significantly correlated with either YSR variable.

With regard to cross-informant analyses, as mentioned above, self-reported secondary control coping was significantly and negatively correlated with CBCL internalizing and externalizing problems ($r = -.46$, $p < .05$ for both; See Table 6). However, neither self-reported primary control coping nor disengagement coping were correlated with either CBCL variable.

With regard to parent-report, both primary and secondary control coping were negatively correlated with CBCL internalizing ($r = -.68$, $p < .01$; $r = -.65$, $p < .01$, respectively) and externalizing behavior problems ($r = -.60$, $p < .01$; $r = -.66$, $p < .01$, respectively; See Table 5). Also as expected, disengagement coping was positively correlated with CBCL internalizing behavior problems ($r = -.66$, $p < .01$). In addition, the

correlation between parent-reported disengagement coping and CBCL externalizing behavior problems approached significance (r = .34, *p* = .07).

Regarding the cross-informant analyses, the correlation between parent-reported secondary control coping and YSR externalizing problems approached significance (r = -.34, *p* = .07; See Table 6). Parent-reported primary control and disengagement coping were not significantly correlated with either YSR variable.

Table 6

Cross-Informant Correlations for Coping and Emotional and Behavioral Problems

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. S-R Primary Control Coping		-.19	**-.63****	.21	.04	-.26	-.26	-.33	.06	.33
2. S-R Secondary Control Coping	.15		-.07	.24	.32+	**-.42***	**-.42***	-.23	-.09	.13
3. S-R Disengagement Coping	**-.42***	**-.62**		-.27	-.22	.25	-.01	.09	-.04	-.25
4. P-R Primary Control Coping	.19	**.47***	**-.43***		-.10	**-.66****	-.23	.01	-.35+	-.18
5. P-R Secondary Control Coping	.18	.29	-.26	**.48****		-.14	-.10	-.08	-.11	-.10
6. P-R Disengagement Coping	-.14	-.26	.23	**-.72****	**-.63****		**.38***	.09	.32	.09
7. YSR Internalizing	**.**01	**-.64****	.20	-.19	-.16	.28		**.54****	**.54****	.08
8. YSR Externalizing	.04	**-.51****	.13	-.17	**-.**34+	.22	**.69****		.07	-.01
9. CBCL Internalizing	-.16	**-.46***	.26	**-.68****	**-.65****	**.66****	**.40***	.33		**.49****
10. CBCL Externalizing	-.15	**-.46***	.30	**-.60****	**-.66****	.34+	.11	.32	**.64****	

Note: Healthy control correlations are on the top right

Healthy Control Group

All correlations among the coping and emotional outcome variables were in the predicted directions for the healthy control group. With regard to self-report, the correlation between primary control coping and YSR externalizing behavior problems approached significance (r = -.33, p = .08; See Table 4). Additionally, a significant negative correlation was found between self-reported secondary control coping and YSR internalizing behavior problems (r = -.42, $p < .05$). Self-reported disengagement coping was not significantly correlated with either YSR variable.

Regarding parent-report, the negative correlation between primary control coping and CBCL internalizing behavior problems approached significance (r = -.35, p = .06; See Table 5). Parent-reported secondary control coping did not correlate significantly with either CBCL variable. A positive correlation between parent-reported disengagement coping and CBCL internalizing behavior problems approached significance (r = .32, p = .09).

Between-Group Comparison of Correlations

Like the preceding two hypotheses, it was predicted that associations among the coping and emotional outcome variables would be stronger for the ALL group than for the control group. Between-group comparisons of significant correlations were conducted using Fisher's z-tests. Three sets of correlations were statistically significant or approached significance in both groups: self-reported secondary control coping and YSR internalizing behavior problems, parent-reported primary control coping and CBCL internalizing behavior problems, and parent-reported disengagement coping and CBCL

internalizing behavior problems. No between-groups differences were found regarding the strength of these relations (z = -1.14, z = -1.70, and z = 1.69, respectively).

Hypothesis 7. The seventh and final hypothesis predicted that coping strategies would mediate the relation between executive function and emotional and behavior problems.

ALL Group

Five sets of variables met criteria to be tested for mediation for the ALL group. That is, coping could only be tested as a mediator between executive function and emotional and behavioral problems for the following five executive function predictors: D-KEFS Sorting Test and the four BRIEF subscales, including Working Memory, Shift, Inhibit, and Monitor (See Tables 7-12).

First, parent-reported primary control coping was tested as a mediator of the relation between the D-KEFS Sorting Test and CBCL internalizing and externalizing problems. The regression equation in which D-KEFS Sorting Test scores predicted CBCL internalizing problems was significantly different from zero, $F(1, 26) = 5.49$, $p < .01$, accounting for 14.3% of the variance in CBCL internalizing problems. Inclusion of parent-reported primary control accounted for an additional 28.8% of the data and resulted in a significant decrease in the relation between D-KEFS Sorting and CBCL internalizing problems such that D-KEFS Sorting was no longer a significant predictor. Therefore, mediation was tested using Sobel's test, which was significant ($z = -2.53$, $p = .01$), indicating a fully mediated model. Likewise, parent-reported primary control

coping fully mediated the relation between D-KEFS Sorting Test and CBCL externalizing problems ($z = -2.35$, $p < .05$).

Second, parent-reported primary control, secondary control, and disengagement coping were each tested as mediators of the relation between each of the BRIEF subscales and CBCL internalizing and externalizing problems. The regression equation in which BRIEF Working Memory scores predicted CBCL internalizing problems was significantly different from zero, $F(1, 26) = 22.66$, $p < .01$, accounting for 44.5% of the variance in CBCL internalizing problems. Inclusion of primary control coping accounted for an additional 8.2% of the variance, $F(2, 25) = 15.11$, $p < .01$, but did not result in a decrease in the relation between BRIEF Working Memory and CBCL internalizing problems. As primary control coping significantly predicted CBCL internalizing problems in the full equation, significant indirect effects were tested using Sobel's test. The indirect effect of BRIEF Working Memory via primary control coping was significantly different from the direct effects ($z = 3.69$, $p < .01$), suggesting that primary control coping partially mediated the relation between BRIEF Working Memory and CBCL internalizing problems. Likewise, parent-reported primary control coping partially mediated the relation between BRIEF Working Memory and CBCL externalizing problems ($z = 3.22$, $p < .01$). In addition, parent-reported secondary control coping partially mediated the relation between BRIEF Working Memory and both CBCL internalizing ($z = 2.16$, $p < .05$) and externalizing problems ($z = 2.19$, $p < .05$). Parent-reported disengagement coping also partially mediated the relation between BRIEF Working Memory and CBCL internalizing problems ($z = 2.55$, $p = .01$) but not externalizing problems ($z = 1.55$, $p =$ ns).

Third, parent-reported primary control, secondary control, and disengagement coping were each tested as mediators of the relation between BRIEF Shift and CBCL internalizing and externalizing problems. The regression equation in which BRIEF Shift scores predicted CBCL internalizing problems was significantly different from zero, $F(1, 26) = 35.64$, $p < .01$, accounting for 56.2% of the variance in CBCL internalizing problems. Inclusion of primary control coping accounted for an additional 17% of the variance, $F(2, 25) = 37.21$, $p < .01$, but did not result in a decrease in the relation between BRIEF Working Memory and CBCL internalizing problems. As primary control coping significantly predicted CBCL internalizing problems in the full equation, significant indirect effects were tested using Sobel's test. The indirect effect of BRIEF Shift via primary control coping was significantly different from the direct effects ($z = 2.20$, $p < .05$), suggesting that primary control coping partially mediated the relation between BRIEF Shift and CBCL internalizing problems. Similarly, parent-reported primary control coping partially mediated the relation between BRIEF Shift and CBCL externalizing problems ($z = 2.49$, $p = .01$). Parent-reported secondary control and disengagement coping also partially mediated the relations between BRIEF Shift and CBCL internalizing problems ($z = 2.25$, $p < .05$ and $z = 2.19$, $p < .05$, respectively). While parent-reported secondary control coping partially mediated the relation between BRIEF Shift and CBCL externalizing problems ($z = 2.23$, $p < .05$), parent-reported disengagement coping did not ($z = 1.80$, $p =$ ns).

Fourth, parent-reported primary control and disengagement coping were tested as mediators of the relation between BRIEF Inhibit and CBCL internalizing and externalizing problems. The regression equation in which BRIEF Inhibit scores predicted

CBCL internalizing problems was significantly different from zero, $F (1, 26) = 5.71$, $p < .01$, accounting for 15% of the variance in CBCL internalizing problems. Inclusion of primary control coping accounted for an additional 26.5% of the variance, $F (2, 25) = 10.57$, $p < .01$ and resulted in a significant decrease in the relation between BRIEF Inhibit and CBCL internalizing problems. Results from Sobel's test indicated that this that parent-reported primary control coping fully mediated the relation between BRIEF Inhibit and CBCL internalizing problems ($z = 2.80$, $p < .01$). Similarly, parent-reported primary control coping partially mediated the relation between BRIEF Shift and CBCL externalizing problems ($z = 2.49$, $p = .01$). Parent-reported disengagement coping partially mediated the relation between BRIEF Inhibit and CBCL internalizing problems ($z = 2.49$, $p = .01$), but this was not the case for the relation between BRIEF Inhibit and CBCL externalizing problems ($z = 1.57$, p = n.s.).

Finally, self-reported secondary control coping and all three of the parent-reported coping factors (primary control, secondary control, and disengagement) were tested as mediators in the relation between BRIEF Monitor and CBCL internalizing and externalizing problems. The regression equation in which BRIEF Monitor scores predicted CBCL internalizing problems was significantly different from zero, $F (1, 26) = 18.96$, $p < .01$, accounting for 38.7% of the variance in CBCL internalizing problems. Inclusion of self-reported secondary control coping accounted for an additional 7.8% of the variance, $F (2, 25) = 13.12$, $p < .01$, but did not result in a decrease in the relation between BRIEF Monitor and CBCL internalizing problems. As self-reported secondary control coping significantly predicted CBCL internalizing problems in the full equation, significant indirect effects were tested using Sobel's test. The indirect effect of BRIEF

Monitor via self-reported secondary control coping was significantly different from the direct effects ($z = 2.89$, $p < .01$), suggesting that secondary control coping partially mediated the relation between BRIEF Monitor and CBCL internalizing problems. Parent-reported primary control, secondary control, and disengagement coping all partially mediated the relation between BRIEF Monitor and CBCL internalizing problems ($z = 3.01$, $p < .01$; $z = 2.90$, $p < .01$; $z = 2.78$, $p < .01$, respectively). Parent-reported secondary control coping partially mediated the relation between BRIEF Monitor and CBCL externalizing problems ($z = 2.50$, $p < .05$), but parent-reported primary control and disengagement coping did not ($z = 1.80$ and $z = 1.67$, respectively, both ns).

Healthy Control Group

Only one set of variables met criteria needed to test for mediation for the healthy control group. Specifically, parent-reported primary control coping was tested as a mediator of the relation between BRIEF Shift scores and CBCL internalizing problems. The regression equation in which BRIEF Shift scores predicted CBCL internalizing problems was significantly different from zero, $F (1, 25) = 9.13$, $p < .01$, accounting for 26.7% of the variance in CBCL internalizing problems. Inclusion of parent-reported primary control coping did not account for a significant increase in the percentage of variance accounted for ($\Delta R^2 = .03$, n.s.) and did not result in a decrease in the relation between BRIEF Shift and CBCL Internalizing problems. Therefore, these results support an independent effect of CBCL internalizing problems by BRIEF Shift scores and do not provide evidence of mediation.

Table 7

Regression Equations Testing Primary Control Coping as a Mediator Between Executive Function and CBCL Internalizing Problems

Equation 1 – CBCL Internalizing		Final R^2 = .42 F (2) = 10.76, p < .01
Step 1: R^2 change = .17*	β	sr
D-KEFS Sorting Test	-.42*	-.41
Step 2: R^2 change = .29**		
D-KEFS Sorting Test	-.09	-.08
P-R Primary Control Coping	-.63**	-.54
Equation 2 – CBCL Internalizing		Final R^2 = .51 F (2) = 15.11, p < .01
Step 1: R^2 change = .47**	β	sr
BRIEF Working Memory	-.68**	-.68
Step 2: R^2 change = .08*		
BRIEF Working Memory	-.41*	-.30
P-R Primary Control Coping	-.39*	-.29
Equation 3 – CBCL Internalizing		Final R^2 = .65 F (2) = 26.18, p < .01
Step 1: R^2 change = .58**	β	sr
BRIEF Shift	-.76**	-.76
Step 2: R^2 change = .10*		
BRIEF Shift	-.56**	-.47
P-R Primary Control Coping	-.37*	-.31
Equation 4 – CBCL Internalizing		Final R^2 = .46 F (2) = 10.57, p <.01
Step 1: R^2 change = .18*	β	sr
BRIEF Inhibit	-.42*	-.42
Step 2: R^2 change = .28**		
BRIEF Inhibit	-.04	-.03
P-R Primary Control Coping	-.71**	-.53
Equation 5 – CBCL Internalizing		Final R^2 = .65 F (2) = 26.23, p <.01
Step 1: R^2 change = .61**	β	sr
BRIEF Monitor	-.78**	-.78
Step 2: R^2 change = .06*		
BRIEF Monitor	-.59**	-.47
P-R Primary Control Coping	-.32*	-.25

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

Table 8

Regression Equations Testing Primary Control Coping as a Mediator Between Executive Function and CBCL Externalizing Problems

Equation 1 – CBCL Externalizing	Final R^2 = .18	F (2) = 7.79, p < .01
Step 1: R^2 change = .20*	β	sr
D-KEFS Sorting Test	-.45*	-.45
Step 2: R^2 change = .18*		
D-KEFS Sorting Test	-.19	-.20
P-R Primary Control Coping	-.50**	-.48
Equation 2 – CBCL Externalizing	Final R^2 = .48	F (2) = 14.00, p <.01
Step 1: R^2 change = .63**	β	sr
BRIEF Working Memory	-.65**	-.63
Step 2: R^2 change = .10*		
BRIEF Working Memory	-.42*	-.33
P-R Primary Control Coping	-.40*	-.31
Equation 3 – CBCL Externalizing	Final R^2 = .52	F (2) = 13.31, p <.01
Step 1: R^2 change = .41**	β	sr
BRIEF Shift	-.66**	-.66
Step 2: R^2 change = .48*		
BRIEF Shift	-.47**	-.40
P-R Primary Control Coping	-.34*	-.29
Equation 4 – CBCL Externalizing	Final R^2 = .45	F (2) = 10.16, p <.01
Step 1: R^2 change = .39**	β	sr
BRIEF Inhibit	-.62**	-.62
Step 2: R^2 change = .06		
BRIEF Inhibit	-.40*	-.30
P-R Primary Control Coping	-.33	-.25
Equation 5 – CBCL Externalizing	Final R^2 = .58	F (2) = 19.49, p <.01
Step 1: R^2 change = .58**	β	sr
BRIEF Monitor	-.76**	-.76
Step 2: R^2 change = .03		
BRIEF Monitor	-.63**	-.50
P-R Primary Control Coping	-.21	-.17

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

Table 9

Regression Equations Testing Secondary Control Coping as a Mediator Between Executive Function and CBCL Internalizing Problems

Equation 1 – CBCL Internalizing		Final R^2 = .54	F (2) = 16.87, p < .01
Step 1: R^2 change = .47**	β	sr	
BRIEF Working Memory	-.68**	-.68	
Step 2: R^2 change = .11*			
BRIEF Working Memory	-.47**	-.40	
P-R Secondary Control Coping	-.39*	-.33	
Equation 2 – CBCL Internalizing		Final R^2 = .67	F (2) = 28.56, p <.01
Step 1: R^2 change = .58*	β	sr	
BRIEF Shift	-.76**	-.76	
Step 2: R^2 change = .12**			
BRIEF Shift	-.59**	-.53	
P-R Secondary Control Coping	-.38**	-.34	
Equation 3 – CBCL Internalizing		Final R^2 = .47	F (2) = 13.12, p <.01
Step 1: R^2 change = .39**	β	sr	
BRIEF Monitor	-.64**	-.64	
Step 2: R^2 change = .08*			
BRIEF Monitor	-.48**	-.42	
S-R Secondary Control Coping	-.33*	-.29	
Equation 4 – CBCL Internalizing		Final R^2 = .68	F (2) = 29.89, p <.01
Step 1: R^2 change = .61**	β	sr	
BRIEF Monitor	-.78**	-.78	
Step 2: R^2 change = .09**			
BRIEF Monitor	-.62**	-.54	
P-R Secondary Control Coping	-.35**	-.30	

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

Table 10

Regression Equations Testing Secondary Control Coping as a Mediator Between Executive Function and CBCL Externalizing Problems

Equation 1 – CBCL Externalizing		Final R^2 = .69	F (2) = 30.47, p < .01
Step 1: R^2 change = .63**	β	sr	
BRIEF Working Memory	-.80**	-.80	
Step 2: R^2 change = .08*			
BRIEF Working Memory	-.62**	-.52	
P-R Secondary Control Coping	-.33*	-.28	
Equation 2 – CBCL Externalizing		Final R^2 = .57	F (2) = 18.94, p <.01
Step 1: R^2 change = .43**	β	sr	
BRIEF Shift	-.66**	-.66	
Step 2: R^2 change = .17**			
BRIEF Shift	-.45**	-.40	
P-R Secondary Control Coping	-.46**	-.41	
Equation 3 – CBCL Externalizing		Final R^2 = .67	F (2) = 27.91, p <.01
Step 1: R^2 change = .58**	β	sr	
BRIEF Monitor	-.76**	-.76	
Step 2: R^2 change = .11**			
BRIEF Monitor	-.58**	-.50	
P-R Secondary Control Coping	-.38**	-.33	

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

Table 11

Regression Equations Testing Disengagement Coping as a Mediator Between Executive Function and CBCL Internalizing Problems

Equation 1 – CBCL Internalizing	Final R^2 = .57	F (2) = 18.51, p < .01
Step 1: R^2 change = .47**	β	sr
BRIEF Working Memory	-.68**	-.68
Step 2: R^2 change = .13**		
BRIEF Working Memory	-.47**	-.41
P-R Disengagement Coping	.42**	.36
Equation 2 – CBCL Internalizing	Final R^2 = .73	F (2) = 37.21, p <.01
Step 1: R^2 change = .58**	β	sr
BRIEF Shift	-.76**	-.76
Step 2: R^2 change = .17**		
BRIEF Shift	-.60**	-.56
P-R Disengagement Coping	.44**	.41
Equation 3 – CBCL Internalizing	Final R^2 = .40	F (2) = 9.82, p <.01
Step 1: R^2 change = .18*	β	sr
BRIEF Inhibit	-.42*	-.42
Step 2: R^2 change = .26**		
BRIEF Inhibit	-.11	-.10
P-R Disengagement Coping	.60**	.51
Equation 4 – CBCL Internalizing	Final R^2 = .70	F (2) = 32.35, p <.01
Step 1: R^2 change = .61**	β	sr
BRIEF Monitor	-.78**	-.78
Step 2: R^2 change = .11**		
BRIEF Monitor	-.61**	-.54
P-R Disengagement Coping	.37**	.33

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

Table 12

Regression Equations Testing Disengagement Coping as a Mediator Between Executive Function and CBCL Externalizing Problems

Equation 1 – CBCL Externalizing		Final R^2 = .61	F (2) = 22.05, p < .01
Step 1: R^2 change = .63**	β	sr	
BRIEF Working Memory	-.80**	-.80	
Step 2: R^2 change = .01			
BRIEF Working Memory	-.84**	-.73	
P-R Disengagement Coping	.09	.07	
Equation 2 – CBCL Externalizing		Final R^2 = .40	F (2) = 10.00, p <.01
Step 1: R^2 change = .43**	β	sr	
BRIEF Shift	-.66**	-.66	
Step 2: R^2 change = .01			
BRIEF Shift	-.62**	-.58	
P-R Disengagement Coping	.12	.11	
Equation 3 – CBCL Externalizing		Final R^2 = .34	F (2) = 7.89, p <.01
Step 1: R^2 change = .39**	β	sr	
BRIEF Inhibit	-.62**	-.76	
Step 2: R^2 change = .00			
BRIEF Inhibit	-.61**	-.52	
P-R Disengagement Coping	.02	.02	
Equation 4 – CBCL Externalizing		Final R^2 = .55	F (2) = 17.33, p <.01
Step 1: R^2 change = .58**	β	sr	
BRIEF Monitor	-.76**	-.76	
Step 2: R^2 change = .00			
BRIEF Monitor	-.78**	-.68	
P-R Disengagement Coping	.03	.02	

Note: P-R = Parent-reported; S-R = Self-reported; β = standardized beta; sr = semi-partial correlation
* <.05, ** < .01

CHAPTER IV

DISCUSSION

This study examined the role of executive function in coping with stress and emotional and behavioral problems in a sample of childhood ALL survivors and a matched sample of healthy controls. It was predicted that ALL survivors would exhibit poorer executive function, less adaptive patterns of coping, and greater emotional and behavioral problems than children with no history of leukemia. In addition, it was expected that coping would mediate the relation between executive function and emotional problems. That is, poorer executive function would lead to greater use of disengagement strategies, such as denial and avoidance, and less reliance on primary control (e.g., problem solving) and secondary control (e.g., acceptance; cognitive restructuring) coping, which would then lead to more internalizing and externalizing behavior problems. This pattern was expected to be true particularly for the ALL group, who are at risk for executive function impairment from their neurotoxic treatment.

With regard to the between-group differences among the executive function, coping, and emotional variables, the data partially support the hypothesis that childhood ALL survivors demonstrate more maladaptive functioning than the healthy control group. Specifically, consistent with the recent meta-analysis published by Campbell and colleagues (in press), ALL survivors had significantly lower scores in several domains of executive function, including working memory, measured behaviorally and by parent-report, as well as a behavioral measure of cognitive flexibility. ALL survivors also

performed more poorly on a test of overall intellectual functioning and a measure of information processing speed. Although not all between-group comparisons of executive function reached statistical significance, effect sizes comparing the ALL and healthy control groups were all in the negative direction, indicating poorer executive function across the various domains and methods of measurement. These effect sizes ranged from negligible to medium, with small effects found for both measures of cognitive flexibility and parent-reported executive inhibition and medium effects found for both measures of working memory. Thus, the results of the present study provide a strong replication of the findings reported by Campbell et al. in their meta-analysis. Other domains of cognitive function, not assessed in the current study, also showed deficits for ALL survivors, indicating that the adverse effects of treatment extend beyond the variables measured here.

There were no statistically significant differences between the groups with regard to the proportion of each type of coping strategy endorsed by children and parents. However, small albeit non-significant, negative effects were found for both self-reported and parent-reported secondary control coping, suggesting ALL participants and their parents tended to endorse comparatively more strategies like acceptance and cognitive restructuring in response to stress than did healthy control participants. Caution must be used interpreting these results, however, since the small sample size did not yield enough power to establish if these small effects are reliable. In general, the present study does not suggest that ALL survivors differ from healthy controls in their patterns of coping with stress.

The ALL and healthy control groups did not significantly differ on self- or parent-reported internalizing or externalizing symptoms. In fact, a small, positive but non-significant effect for CBCL internalizing symptoms was found, suggesting that ALL survivors experience less emotional distress, such as symptoms of depression and anxiety, than do children with no history of leukemia. This finding is consistent with previous research that suggests that childhood cancer survivors are emotionally doing as well, if not better than healthy children (e.g., Phipps, Steele, Hall, & Leigh, 2001; Recklitis et al., 2006). Whether such findings truly indicate that ALL survivors experience little or no symptoms of psychopathology is still being debated in the field of pediatric psycho-oncology. Phipps and colleagues at St. Jude posit that cancer survivors, along with other pediatric patients diagnosed with chronic illnesses, such as Type I diabetes, cystic fibrosis, and juvenile rheumatoid arthritis, have a repressive adaptational style, which is characterized by a denial of personal problems or flaws, including psychological distress, and an endorsement of socially desirable behavior, which may be interpreted as defensiveness (e.g., Phipps & Steele, 2002; Phipps, Steele, Hall, & Leigh, 2001). Testing this theory is beyond the scope of the current study; however, it is important to consider the current findings in light of this theory. One study by Phipps and colleagues (2001) found that childhood cancer patients exhibit a repressive adaptational style within 2 to 4 weeks of diagnosis, which the authors concluded is a reaction to the diagnosis rather than a premorbid personality trait. If the current study findings reflect the phenomenon of repressive adaptation, this would suggest that children treated for ALL continue exhibiting this style well after their treatment ends.

However, when the CBCL and YSR internalizing and externalizing problem scales were further delineated into the various syndrome scales in the current study's analyses, the picture is less clear. Small, negative effects were found for some of the CBCL and YSR scales, suggesting more problems for the ALL survivors, and small, positive ones were found for others. However, these findings differed depending on whether the parent or child reported the problems. Specifically, according to parent report on the CBCL, ALL survivors appear to have more difficulties than healthy controls with regard to social problems, attention problems, and rule-breaking behaviors, but that they actually exhibit fewer somatic symptoms than healthy controls. In contrast, according to the reports of the children and adolescents on the YSR, ALL survivors endorsed more difficulties with symptoms of anxiety and somatic problems, whereas they endorse fewer depressive symptoms, social problems, and aggressive behavior than do healthy controls. In short, the question about whether childhood cancer survivors experience emotional and behavioral problems seems to depend on the informant and what specific problems are assessed. However, because of limited statistical power, comparison of the ALL and healthy control groups on these more specific indicators of types of emotional and behavioral problems did not reach statistical significance. Future research with larger samples is needed to examine some of the trends observed in the present data to determine if there are differences between ALL survivors and healthy controls in specific domains of psychological problems.

Although the current study did not find significant between-group differences on all variables examined in this study, it is noteworthy that there were many more statistically significant correlations among the executive function, coping, and

emotional/behavioral variables for the ALL group compared to the healthy control group. While many of these correlations were among the parent-reported independent and dependent measures (BRIEF executive function, parent-reported coping on the RSQ, and CBCL internalizing and externalizing behaviors), indicating that shared-method variance played a role in these associations, there was also evidence of important associations across informants and method of measurement. These are briefly summarized here, as they are considered more robust findings.

Self-reported secondary control coping was significantly and positively correlated with all four parent-reported domains of executive function: working memory, cognitive flexibility, behavioral inhibition, and self-monitoring. In addition, self-reported disengagement coping was significantly and negatively correlated with both behavioral and parent-report measures of working memory and self-monitoring, and parent-reported behavioral inhibition. Parent-reported primary control coping was significantly and positively correlated with the behavioral measures of working memory and cognitive flexibility, and parent-reported disengagement coping was significantly and negatively correlated with the behavioral measure of working memory. These findings support the theory that coping is governed by executive function processes and is therefore regulated by the dorsolateral prefrontal cortex and its cortical and subcortical connections thought to be responsible for higher-order cognitive functioning (Compas, 2006; Copeland & Compas, 2007).

With regard to the correlations among the executive function and emotional/ behavioral variables, significant findings were also found across informants and methods. Specifically, self-reported internalizing behavior problems were significantly associated

with parent-reported self-monitoring, and self-reported externalizing behavior problems were significantly associated with behavioral measures of behavioral inhibition and working memory. Both parent-reported internalizing and externalizing problems were significantly associated with the behavioral measure of cognitive flexibility. Finally, regarding the correlations among coping and emotional/behavioral variables, self- and parent-reported secondary control coping were associated with self- and parent-reported externalizing behavior problems. Self-reported secondary control coping was also significantly associated with parent-reported internalizing problems. These correlations suggest that impairment in executive functioning, coping, and emotion regulation resulting from neurotoxic ALL treatment is related to increases in emotional and behavioral problems in childhood ALL survivors.

Most importantly, the data provide some support for the hypothesis that coping mediates the relation between executive function and emotional outcome in survivors of childhood ALL. As expected, the majority of the mediation analyses were tested among the parent-reported executive function, coping, and emotional/behavioral variables, again suggesting shared method variance. However, there were also two instances of mediation across methods or informants. The findings regarding the mediation analyses are summarized below.

First, primary control coping, as reported by the parents of ALL survivors, fully mediated the relations between the behavioral measure of cognitive flexibility and parent-reported internalizing and externalizing behavior. Primary control coping also fully mediated the relation between parent-reported behavioral inhibition and parent-reported internalizing behavior. Consistent with the findings reported by Copeland and Compas

(2007), these findings suggest that difficulties switching back and forth between tasks and the inability to inhibit one's prepotent responses leads to the use of less problem-solving, emotional modulation, and emotional expression in coping with stress, which in turn leads to emotional distress and perhaps even behavior problems.

All other findings indicated partial mediation, meaning that although coping appears to play an important role in the relation between executive function and emotional/behavioral outcomes, there is also a direct relation between these variables independent of coping. Both self- and parent-reported secondary control coping partially mediated the relation between parent-reported self-monitoring and parent-reported internalizing behavior. Similarly, parent-reported secondary control coping partially mediated the relations between the following parent-reported executive functions: working memory; cognitive flexibility; behavioral inhibition and internalizing/externalizing behavior problems. These findings suggests that poorer executive function in several domains leads to decreased use of cognitive restructuring and acceptance and/or increased reliance on maladaptive patterns of coping, such as denial and avoidance, which then leads to emotional distress. The fact that a direct relation remains between executive function internalizing/externalizing behaviors may also mean that difficulties in working memory, self-monitoring, cognitive flexibility, and behavioral inhibition lead to other factors that are not accounted for in this study, such as an increase of cognitive distortions or difficulties in attention, that then leads to emotional and behavioral problems. Another interpretation of the direct relation is that a neurophysiological process occurring in the prefrontal cortex or white matter leads to impaired executive functioning and emotional dysregulation.

It is possible that one reason the ALL group evinced more important relations among the executive function, coping, and emotional/behavioral variables despite the lack of statistically significant between-group findings is that only a subgroup of childhood ALL survivors experience executive function deficits as a result of their treatment, which is associated with less adaptive patterns of coping with stress and emotional difficulties. Research with adult cancer survivors is instructive with regard to possible individual differences in vulnerability to the adverse effects of chemotherapy. Research examining the neurocognitive sequelae of adult cancer treatment, a phenomenon referred to as "chemobrain," suggests that adults who carry a genetic marker for Alzheimer's disease (ε4 allele of the APOE gene), may be at increased vulnerability to chemotherapy-induced neurocognitive impairment compared to adult cancer survivors who were not carriers of the gene (Ahles et al. 2003). Further, Ahles and Saykin (2007) also discuss other potential mechanisms by which individuals treated with chemotherapy experience cognitive changes, such as DNA damage and deficits in DNA repair, as well as deregulation of the immune response caused by neurotoxic treatments. Although this work has been done in survivors of adult cancers, such as breast and lung neoplasms, it is possible that a subset of children treated for cancers, including leukemia, with chemotherapy agents may possess similar vulnerabilities to cognitive impairment.

Strengths of the Current Study

Methodologically, the current study went beyond previous studies examining the neurocognitive sequelae of childhood cancer in several ways. First, the sample of

childhood cancer survivors was homogeneous with regard to diagnosis, type of treatment received, and stage of treatment. That is, only children and adolescents who were successfully treated for a first diagnosis of ALL with chemotherapy only and were off treatment by the time of study participation were included. Many studies in the literature have combined patients with different types of leukemias and have frequently included lymphomas in the study sample despite the fact that these diagnoses are very different in terms of their prognoses, type of treatment, and length of treatment. Likewise, it is not uncommon for children with CNS tumors to be included in the same study sample as leukemia patients. Further, all of the ALL participants in the current study completed treatment prior to recruitment, whereas some studies include patients who are still receiving ALL treatment with those who are off treatment, making it difficult to distinguish acute, temporary cognitive disturbance related to certain types of chemotherapy to long-term neurocognitive sequelae.

Another methodological strength of the current study was the selection of a healthy control sample matched to the ALL participants on sex, age, and when possible, socioeconomic status in an effort to reduce the number of confounding variables. Although the groups matched very well with regard to household income, the primary caregivers in the healthy control group had significantly higher educational attainment than did the parents in the healthy control sample. However, even when educational status was controlled for in the analyses, there were still significant differences between the groups on Full Scale IQ and both measures of working memory, indicating that the between-group differences in neurocognitive functioning were not solely attributable to the difference in parent education.

Additionally, the study employed multiple methods (behavioral assessment and parent report of executive function), as well as multiple informants (child and parent report of coping and emotional/behavioral symptoms). Both of these methodological strengths are essential in better understanding the factors contributing to the neurocognitive and emotional sequelae of childhood ALL.

Another important strength of this study was that it employed measures of specific domains of executive function with a normative sample of participants. Previous studies examining ALL treatment effects on executive function used a variety of measures assessing various domains of executive function, making it difficult to compare studies or generalize findings given that few studies defined "executive function" in the same way. In addition, a variety of norms to interpret the data yielded from these studies were used, many of which were comprised of very small sample sizes. The D-KEFS, was normed on a sample of 1,750 individuals stratified by age and produces standard scores for each of its subtests, making the results comparable and easily interpretable.

Limitations of the Current Study

The current study also had several limitations that must be addressed. First, as noted throughout this paper, the sample size of 30 participants in each group limited power to detect smaller but potentially meaningful effects, both in regard to between-group findings and correlations among the variables within each group. Effect sizes were reported in order to demonstrate potentially meaningful findings, which will need to be corroborated by adding more participants and thus increasing power. It should be noted, however, that this study's sample of childhood ALL survivors is on par with or larger

than 50 to 60% of the published papers included in the meta-analysis reviewing the neurocognitive effects of childhood ALL treatment (Campbell et al., in press). Given the relatively low base rate of childhood cancer and most other pediatric disorders, collaborative studies among multiple institutions are essential in recruiting large samples of children treated for a specific illness. The research team working on the current study plans to continue recruiting participants and is considering partnering with research teams at other academic children's hospitals.

As mentioned above, although the healthy control sample was matched exceptionally well with regard to sex, age, and family income, the healthy control parents had a greater level of educational attainment. Approximately 75% of the healthy control participants and their parents were recruited through the Vanderbilt Medical Center, and as a result, the majority of those who volunteered for this study worked in professional positions. The other method of recruitment asking ALL participants to nominate same-age, same-sex friends and classmates, only yielded 25% of the healthy control sample, as many of the ALL survivors declined this method.

Clinical Implications

The results from this study suggest that the neurocognitive sequelae of childhood ALL extend beyond academic and vocational outcomes. The preliminary results of this study partially support the assertion that impaired executive function in at least a subset of childhood ALL survivors may limit their ability to effectively cope with stress. These findings demonstrate the necessity of intervention techniques that teach childhood cancer survivors cognitive-behavioral and metacognitive techniques (Butler & Copeland, 2002),

as well as other coping skills, not solely for the goal of cognitive remediation and improves school performance, but also to prevent emotional problems that could result from maladaptive patterns of coping.

Additionally, there is some evidence in the literature to suggest that childhood ALL survivors, particularly during adolescence, are susceptible to social problems with peers (e.g., Shelby et al., 1998). The current study assessed coping strategies specifically with regard to social stressors, as it is a common source of stress for all adolescents, healthy or ill. Some of the findings suggested that the ALL survivors in this study used fewer adaptive coping strategies, such as problem-solving and cognitive restructuring and relied more on avoidance and denial in response to normative social stressors, such as arguing with a friend or feeling left out. Barakat and colleagues (2003) created a manualized group intervention for survivors of pediatric brain tumors and their parents, and preliminary findings demonstrated small to moderate improvements in social skills (e.g., nonverbal communication; engaging in conversation) and social functioning. Such an intervention might be equally beneficial for the subset of ALL survivors that evince peer-related problems.

Directions for Future Research

This study paves the way for continued research on the relation between neurocognitive impairment and coping in children treated for ALL. The research team for the current study is continuing to recruit participants to increase the sample size and improve power, which will enable us to better interpret the data. However, the preliminary data presented in this paper already highlight the importance of examining

childhood cancer survivors' ability to cope with life stress, especially given their risk for neurocognitive problems that can impair their ability to cope and regulate their emotions.

In addition, another study that is currently underway in our laboratory is using structural and functional imaging, as well as DTI, to further examine the neurophysiological underpinnings of executive function impairment, coping, and emotion regulation. Those ALL survivors from the current study who demonstrate significant deficits in executive function during the neurocognitive assessment, as well as their matched healthy controls, are being recruited to participate in the imaging study and will be administered a series of executive function tasks while functionally measuring activation in the prefrontal cortex. This is an important addition to the study, as it is expected to demonstrate specific neurophysiological effects of treatment in ALL survivors that will be associated with poorer performance on the neurocognitive tests administered for the current study.

Finally, research by Ahles and colleagues (2003, 2007) examining genetic markers for "chemobrain" in adults should be extended to survivors of childhood ALL and other pediatric cancers, as it appears that only a subgroup of children receiving neurotoxic therapeutic agents end up with neurocognitive impairment.

Conclusion

The first portion of this study was a replication and extension of previous research comparing ALL survivors to healthy controls with regard to executive function. Consistent with a recently published meta-analytic review (Campbell et al. in press), ALL survivors performed more poorly than healthy controls on several domains of executive

function, even when differences in parent education were taken into account. The results of this study also provide preliminary evidence that some survivors of childhood ALL are susceptible to impaired executive function and therefore experience difficulties in coping effectively with stressful life events, leading to emotional distress and behavior problems. This study asserts that the ability to employ adaptive coping skills is dependent on intact executive functioning, including the domains of working memory, cognitive flexibility, self-monitoring, and behavioral inhibition. When the ability to perform these higher-level cognitive tasks is damaged, children and adolescents appear to rely more heavily on maladaptive patterns of coping, such as denial and avoidance, and less on strategies considered more adaptive, such as problem-solving, acceptance, and cognitive restructuring.

APPENDICES

Appendix A

Demographic Intake Form

Thank you for agreeing to help us with this study. We appreciate you taking time to come into the clinic today. We would like to ask you some questions about your child's life. Some questions ask about your family, your child's health, and progress in school. You should know that everything you say will be kept private and will only be seen by people working on our study. If you aren't sure about the answer to a question, you might have to take your best guess. That's OK. Also, if you don't feel comfortable answering a question it's OK to skip it. Do you have any questions before we get started?

Today's Date: __/__/____ (mm/dd/yyyy)

Examiner: _____

Historian (circle one): Mother Father Stepmother Stepfather
Other (please list relationship):_____

Child's Sex (circle one): Female Male

Child's Age: _____

Child's Date of Birth: __/__/____ (mm/dd/yyyy)

Demographic and Family Information

First I am going to ask you some questions about [*child's name*] home and family life…

1. Who is the child's main caregiver? Mother Father Stepmother Stepfather
   Other (please list relationship):_____
2. What is the date of birth of the main caregiver? __/__/____ (mm/dd/yyyy)
3. What is the date of birth of the child's biological mother (if not the main caregiver)?
   __/__/____ (mm/dd/yyyy)
4. Which of the following best described the child's race or ethnicity?
   ____White or Caucasian
   ____Black or African-American
   ____Latino or Hispanic
   ____Asian, Asian American, or Pacific Islander
   ____Native American or Alaska Native

____Or something else, please describe: _____

5. Which of the following best described the main caregiver's race or ethnicity?
   ____White or Caucasian
   ____Black or African-American
   ____Latino or Hispanic
   ____Asian, Asian American, or Pacific Islander
   ____Native American or Alaska Native
   ____Or something else, please describe: _____
6. Which of the following best described the biological mother's race or ethnicity (if not the main caregiver)?
   ____White or Caucasian
   ____Black or African-American
   ____Latino or Hispanic
   ____Asian, Asian American, or Pacific Islander
   ____Native American or Alaska Native
   ____Or something else, please describe: _____

7. How many siblings does [*child's name*] have? _____

   If he/she has siblings, please list their first name, gender, and age below:

Name	Gender	Age

8. How many people, including both children and adults currently live in the same house as [*child's name*]? _____

9. Which best describes the marital status of the child's main caregiver?
   ____Married/partnered
   ____Separated
   ____Divorced
   ____Widowed
   ____Single/Never Married

10. Which best describes the marital status of the child's biological mother (if not the main caregiver)?
    ____Married/partnered
    ____Separated
    ____Divorced
    ____Widowed
    ____Single/Never Married

11. What is the highest grade or level of school of the main caregiver?
    ____Grade School (grades 1-8)
    ____High School, but didn't graduate

____High School, graduated or obtained GED
____Training after high school, other than college
____Some College
____College Graduate
____Post Graduate Level

12. What is the highest grade or level of school of the biological mother (if not the main caregiver)?
____Grade School (grades 1-8)
____High School, but didn't graduate
____High School, graduated or obtained GED
____Training after high school, other than college
____Some College
____College Graduate
____Post Graduate Level

13. **For this question, please check the box next to the letter that best described your family's income.**

	1	Less than $10,000
	2	$10,000 to $20,000
	3	$20,000 to $30,000
	4	$30,000 to $40,000
	5	$40,000 to $50,000
	6	$50,000 to $60,000
	7	$60,000 to $70,000
	8	$70,000 to $80,000
	9	More than $80,000
	10	I don't know
	11	I'd rather not say

14. What is the job of the person contributing most to the family income? _____

<u>Developmental and Medical History</u>

Now I'd like to ask you some questions about [*child's name*] medical history since he/she was born...

1. How long did the pregnancy with [*child's name*] last? (Full term = 40 weeks) _____ weeks

2. How much did your child weigh at birth? ____ lbs ____ oz

3. Has your child had any other serious medical problems that required hospitalization (IF ALL PARTICIPANT, say ***in addition to ALL***)? ____Yes _____No

If yes, please describe: _____
_____
_____

4. Has your child ever experienced a head injury that led to loss of ____Yes _____No

consciousness and/or hospitalization?

If yes, please describe: _____
_____
_____

5. Has [*child's name*] ever taken any medications for ADD or ADHD ____Yes _____No (e.g., Ritalin, Adderall, Concerta)

   If yes, please list each medication, the reason it was prescribed, approximate start and end dates, whether the child is currently taking the medication, and if it was taken today record the approximate time it was taken.

Medication	Reason Prescribed	Start Date	End Date	Current (Time?)

6. Has your child ever been diagnosed and/or treated for any psychological problems, such as depression or anxiety?

   If yes, please describe the diagnosis and type of treatment: _____
   _____
   _____

   If medication was required, please list each medication, the reason it was prescribed, approximate start and end dates, whether the child is currently taking the medication, and if it was taken today record the approximate time it was taken.

Medication	Reason Prescribed	Start Date	End Date	Current (Time?)

Educational Information

Lastly, I would like to ask you some questions about [*child's name*] education…

1. Is [*child's name*] currently attending school? ____Yes _____No

   If yes, what grade is he/she currently in? _____

2. Has your child ever repeated a grade? ____Yes _____No

   If yes, what grade(s) and why?_____

   If graduated or dropped out, indicate highest grade completed: _____

   If dropped out, obtained GED? ____Yes _____No

3. **ALL PARTICIPANTS ONLY: During ALL treatment, did your child receive any special education services?** ____Yes _____No

   If yes, please explain the services used: _____
   _____
   _____

4. **ALL PARTICIPANTS ONLY: Since ALL treatment, has your child receive any special education services?** ____Yes _____No

   If yes, please explain the services used: _____
   _____
   _____

5. **ALL PARTICIPANTS ONLY: Did your child receive brain scans (e.g., MRI, CT) before, during, or after ALL treatment?** ____Yes _____No

   If yes, please explain: _____
   _____
   _____

6. Has your child ever had an educational or neuropsychological evaluation like what we'll be doing today? ____Yes _____No

   If yes, when and why? _____
   _____

Appendix B

Letter for ALL Participant Recruitment

Dear [Caregiver's Name]:

I am writing on behalf of the Pediatric Hematology/Oncology Division at Vanderbilt Children's Hospital, which is currently studying leukemia (ALL) in childhood and the factors that may influence children's quality of life after treatment.

We know ALL therapy can cause immediate side effects like low blood counts, vomiting, and infections. Researchers would like to learn more about the possible long-term effects from ALL therapy. We are asking children 10-17 years of age who have completed treatment for ALL and their parents to participate in a study looking at the possible effects of chemotherapy on children's memory, problem solving skills, and the ways that they manage their emotions.

We are inviting you to participate in a study at Vanderbilt Children's Hospital. Taking part in this study involves two appointments scheduled on separate days. You and your child can decide to participate in one or both parts of the study—it is completely up to you. During the first appointment, you and your child would be asked to complete questionnaires regarding your child's emotional and behavioral well-being and coping skills and to answer some questions about your child's medical, school, and family life in an interview format. That day your child would also be administered six tests to measure his/her memory and problem-solving skills. If you decide to participate in this part of the study, we will give your child and your child's primary caregiver $25 each as a thank-you for participating, and $10 to help offset some of the costs of travel.

During the second appointment, your child would take a similar set of tests but this time they would complete the tests while our research team uses a scanner to take images (pictures) of his/her brain while responding to test items. This is called functional brain imaging. It is a procedure that uses a large magnet to take pictures of the brain to show how the brain works while it is actively responding to a test or other task. In addition to the tests your child would watch 5 minutes of two movies to see how he/she responds to something that is emotional. If you decide to participate in this second part of the study, your child will receive and additional $25, and your child's primary caregiver will be reimbursed another $10 for travel costs.

There may or may not be a direct benefit to you or your child from taking part in this study. Your child will receive a limited evaluation of his or her learning and thinking abilities, and you will be able to talk to a psychologist about the results. We will also provide you a brief written summary of the test results that you may keep. Because the research exam is different from a complete evaluation, it is possible that the psychologist would recommend further testing. This wouldn't be part of the study, but we would

identify options that are available to you and your child. Overall, it is hoped that the information learned from this study may help future patients who have ALL.

All of the information we collect for the study will be kept strictly coinfidential, and your name and your child's name will not be used in any publication of our findings. Participating in this study is entirely voluntary and your decision to participate or not won't change your relationship with our clinic or Vanderbilt Children's Hospital. Also, if you decide to participate, you may withdraw at any time without prejudice.

Please feel free to call me at (615) 936-1762 if you have any questions or would like to participate. Otherwise, I will call you in several days to answer any questions you may have and determine if you are willing to participate.

Best Regards,

Sue Alisanski, M.D.

Appendix C

Informed Consent Forms

This informed consent applies to parents/guardians of children 10-17 years old.

Name of participant:
_____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because your child was treated for Acute Lymphocytic Leukemia (ALL) at Vanderbilt Children's Hospital. The treatments used for ALL may affect children's memory, learning, attention, thinking, and reasoning.

The goals of this study are:

- To look at neurobehavioral function (in other words, thinking function, learning abilities, and behavior) in patients previously treated for ALL.
- To see if other factors (such as gender, age at diagnosis, and how long it has been since the patient's cancer treatment) are associated with greater neurobehavioral problems in patients treated for ALL; and
- To find if there is a connection between neurobehavioral problems and a patient's happiness with life.

2. What will happen and how long will you be in the study?

Taking part in this study involves two parts:

Part I:
- taking several tests to see if your child has any learning or memory problems which may have developed as a result of the cancer and its treatment;
- filling out a survey to see how happy your child is with his/her life;
- this part of the study will take approximately 3 ½ hours.

Part II:
- having images taken of your child's brain while he/she is performing certain memory and problem-solving tasks and watching two scenes from a movie that are tense or a little bit scary. The images will be taken by a magnetic resonance scanner, which uses magnetic fields to take pictures of the brain;
- this part of the study will take you and your child about 3 hours.

In addition, we would like to collect some medical information from your child's medical records about how your child's child cancer diagnosis and treatment and whether your child is currently free of cancer and other major medical illnesses. By signing this form, you are giving us permission to extract this information from your child's medical record.

3. Costs to you if you take part in this study:

There will be no cost to you or your insurance plan if your child takes part in this study.

4. Side effects and risks that you can expect if you take part in this study:

Your child may find some of the tests boring or tiring. Your child may also become frustrated because some portions of the testing are difficult. The testing may find that your child has problems in thinking, learning, or behavior.

This information could be distressing to you or your child. If your child is found to have results that are lower than expected, the doctor will strongly recommend further testing and will assist you with a referral to an appropriate provider.

Participants with the following may not be able to have an MRI: implanted medical devices such as aneurysm clips in the brain, heart pacemakers and cochlear (inner ear) implants, iron-based tattoos, pieces of metal close to or in an important organ (such as the eye). Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the MRI scanner or may be pulled away from the body in the MRI room. Also, metal can sometimes cause poor pictures if it is close to the part being scanned. For these reasons, patients are asked to remove these objects before going into the MRI room.

Your child will hear "hammering" noises while the scanner is preparing for scanning and taking the pictures. Earplugs will be given to help reduce the noise. Your child may also feel some vibration and some slight movement of the table during the test.

In this study, the fMRI scan is used for research purposes only. However, in the event that an abnormality is found, you will be told and encouraged to consult your child's doctor.

5. Risks that are not known:

There are no unknown risks as a result of taking part in this study.

6. Payment in case you are injured while in this study:

Immediate necessary care in the rare case of an adverse event will be provided at Vanderbilt University without charge if you are injured because of participation in this research project. Vanderbilt will neither provide for the costs of further treatment beyond immediate necessary care nor provide monetary compensation for such injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that <u>might</u> result from this study are: What we learn from this study may help future patients who have leukemia.

b) The benefits you might get from being in this study are: You and your child may or not benefit from taking part in this study. The study evaluation may find problems in thinking, learning, or behavior in your child that may otherwise not have been found. The psychologist will discuss the findings of the evaluation directly with you. You will also be given a typed report that will be yours to keep and to share, if you choose, with others who have an interest

in your child's well-being (such as your child's teacher). We want to stress that this is a research evaluation and not a comprehensive clinical assessment. Further testing may be needed to obtain a complete picture of your child's strengths and as well as the appropriate recommendations for possible services.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to have your child take part in this study. You may want to discuss this with your child's regular doctor as well as other trusted personal and family advisors.

9. Payments for your time spent taking part in this study or expenses:

You and your child will each receive $25 as a thank-you gift for participating in Part I of the study. Your child will receive $40 as a thank-you gift for participating in Part II of the study and you will be given $10 to cover the cost of travel, parking, meals or other costs incurred to come for the testing.

10. Reasons why the study doctor may take you out of this study:

There are no known reasons why your doctor would take your child out of this study. However, if your child is taken out of the study, you will be told the reason.

11. What will happen if you decide to stop being in this study?

You can remove your child from the study or your child can decide to withdrawal at any time. You can either tell the research assistant working with you at ANY time during Part 1 or 2 of the study or you can call Principal Investigator Bruce Compas, Ph.D. at 615-322-8306.

12. Who to call for any questions or in case you are injured:

If you have any questions about this research study or if you feel your child has been hurt by being in this study, please feel free to contact Project Coordinator Laura Keys at 615-343-8720 or Principal Investigator Bruce E. Compas, Ph.D. at 615-322-8306.

For additional information about giving consent or your rights as a person in this study, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273, or email at http://mcapps01.mc.vanderbilt.edu/IRB/WkshpReg.nsf/Suggestion Form?OpenForm.

13. Confidentiality:

All reasonable efforts will be made to keep your child's protected health information (PHI) private and confidential. PHI is individually identifiable health information that is, or has been collected or maintained by Vanderbilt University Medical Center (VUMC), including information that is collected for research purposes only, and can be linked back to you or your child. Using or sharing ("disclosure") such information must follow federal privacy guidelines.

By signing the consent document for this study, you are giving permission ("authorization") for the uses and disclosures of your personal health information. A decision to participate in this research means that you agree to let the research team use and share your child's PHI as described below.

As part of the study, Dr. Compas and his study team may share the results of your child's study test results and non-study related information about your child's diagnosis and treatment, as well

as portions of your child's medical record, with the groups named below. These groups may include representatives from the Federal Government Office for Human Research Protections and the Vanderbilt University Institutional Review Board. Federal privacy regulations may not apply to these groups; however, they have their own policies and guidelines to assure that all reasonable efforts will be made to keep your child's personal health information private and confidential.

The study results will be retained in your child's research record for at least six years after the study is completed. At that time, the research information not already in your child's medical record will be will be destroyed. Any research information entered into your child's medical record will be kept indefinitely.

Unless otherwise indicated, this permission to use or share your child's PHI does not have an expiration date. If you decide to withdraw your permission, we ask that you contact Dr. Compas in writing and let him know that you are withdrawing your permission. His mailing address is: Vanderbilt University, Department of Psychology & Human Development, Peabody College #512, 230 Appleton Place, Nashville, TN 37203. At that time, we will stop further collection of any information about your child. However, the health information collected prior to this withdrawal may continue to be used for the purposes of reporting and research quality.

A decision to not participate in this research study will not affect your child's treatment, payment or enrollment in any health plans or affect your eligibility for benefits. You will receive a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS STUDY

Please

[ ] I have read this consent form and all my questions have been answered.

[ ] The information in this consent form has been explained to me and all my questions have been answered.

[ ] I freely and voluntarily choose to participate in this study. I understand that I may withdraw at any time.

[ ] I freely and voluntarily choose to take part only in Part I of this study (psychological testing and completing questionnaires).

[ ] I freely and voluntarily choose for my child to take part in Part II of this study (brain imaging study).

[ ] I freely and voluntarily choose to allow my child participate in this study. I understand that my child may withdraw at any time and I may withdraw my child at any time.

[ ] I freely and voluntarily choose to allow the research team to contact me by telephone or mail about future research studies examining psychological issues related to childhood cancer.

_____ _____

Date Signature of patient/volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title

This assent document applies to children 10-17 years old.

Name of participant _____Age_____

Below are the answers to some of the questions you may have. If you have any questions about what is written below or have any other questions about this research, please ask them. You will be given a copy of this consent form.

1. Why are you doing this research?

You received medicine to help treat your leukemia. The drugs you got can sometimes have side effects. Some side effects show up right away (like being tired) and others show up later. Not everyone has these side effects, but some people might. All kids are different.

Doctors want to know if kids who have had leukemia treatment have any trouble with things like remembering, learning new things, or paying attention, and this is why we are doing this research.

2. What will I do and how long will it take?

We are asking you to take some skills tests. This will take about 3 ½ hours. We are also asking you to take some tests while you are in a machine that is able to take pictures of your brain. This is called "brain imaging." The machine will take pictures to show how your brain works while you take the tests and while you watch some short movie scenes. The movie scenes might be a little bit scary. This second part of the study takes about 3 hours.

As a thank-you for participating, you will get $25 for taking the skills tests and another $40 for doing the second part of the study where we use a machine to take pictures of your brain.

3. Do I have to be in this research study and can I stop if I want to?

You can choose whether or not you want to be in this research study. You can also stop at ANY time. You can skip a question or a test if you want to and nobody will be mad at you. You can also choose to do just one part of the study.

4. Could it make me sick [or sicker]?

No, but sometimes testing can be a little tiring or difficult. You can take breaks between tests if you start feeling tired or frustrated.

5. Will anyone know that I am in this research study?

No. Your answers will be kept private. Only the people working on our study will see your tests and forms. Your name will not be on any of the tests.

6. How will this research help me or other people?

This research will help doctors find out if cancer drugs affect how kids learn and think. This research could help future leukemia patients. Also, the results of the study might help find some areas of thinking and learning that are more difficult for you. If this happens, we would tell you and your parents how to find out more about these problems.

7. Who do I talk to if I have questions?

If you have any questions about this research study, you can ask your doctors now, or you can call Dr. Bruce Compas (615) 322-8306 or Dr. Debbie Van Slyke at (615) 936-0272.

[ ] I would like to do Part I of this study (skills tests).

[ ] I would like to do Part II for this study (brain imaging).

_____ _____

Date Signature of patient/volunteer

Assent obtained by: _____

Signature Printed Name and Title

This informed consent applies to parents/guardians of children 10-17 years old.

Name of participant: _____
Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

We are conducting this study to learn about the development of learning, memory, and problem-solving skills during childhood and adolescence. We are also interested in how these areas of thinking are related to the ways in which they handle their emotions. In addition to generally healthy participants like your child, we are also asking people who were treated for childhood cancer to be in this study because we want to learn about how their treatment may effect their cognitive development. We will be comparing results from healthy participants and childhood cancer survivors to see if there are differences in thinking, learning, and coping between these two groups.

2. What will happen and how long will you be in the study?

Taking part in this study involves two parts:

Part I:
- taking several tests of learning, memory, and problem-solving
- filling out a survey to see how happy your child is with his/her life;
- this part of the study will take approximately 3 ½ hours.

Part II:
- having images taken of your child's brain while he/she is performing certain memory and problem-solving tasks and watching two scenes from a movie that are tense or a little bit scary. The images will be taken by a magnetic resonance scanner, which uses magnetic fields to take pictures of the brain;
- this part of the study will take you and your child about 3 hours.

3. Costs to you if you take part in this study:

There will be no cost to you or your insurance plan if your child takes part in this study.

4. Side effects and risks that you can expect if you take part in this study:

Your child may find some of the tests boring or tiring. Your child may also become frustrated because some portions of the testing are difficult. The testing may find that your child has some difficulty in thinking, learning, or behavior.

This information could be distressing to you or your child. If your child is found to have results that are lower than expected, we will assist you with a referral to an appropriate provider who

can do further testing, as the testing for this study is not a comprehensive battery that can be used by itself for clinical purposes.

Participants with the following may not be able to have an MRI: implanted medical devices such as aneurysm clips in the brain, heart pacemakers and cochlear (inner ear) implants, iron-based tattoos, pieces of metal close to or in an important organ (such as the eye). Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the MRI scanner or may be pulled away from the body in the MRI room. Also, metal can sometimes cause poor pictures if it is close to the part being scanned. For these reasons, patients are asked to remove these objects before going into the MRI room.

Your child will hear "hammering" noises while the scanner is preparing for scanning and taking the pictures. Earplugs will be given to help reduce the noise. Your child may also feel some vibration and some slight movement of the table during the test.

In this study, the fMRI scan is used for research purposes only. However, in the event that an abnormality is found, you will be told and encouraged to consult your child's doctor.

5. Risks that are not known:

There are no unknown risks as a result of taking part in this study.

6. Payment in case you are injured while in this study:

Immediate necessary care in the rare case of an adverse event will be provided at Vanderbilt University without charge if you are injured because of participation in this research project. Vanderbilt will neither provide for the costs of further treatment beyond immediate necessary care nor provide monetary compensation for such injury.

7. Good effects that might result from this study:

What we learn from this study may help future children and adolescents with learning or other school-related problems.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to have your child take part in this study.

9. Payments for your time spent taking part in this study or expenses:

You and your child will each receive $25 as a thank-you gift for participating in Part I of the study. Your child will receive $40 as a thank-you gift for participating in Part II of the study and you will be given $10 to cover the cost of travel, parking, meals or other costs incurred to come for the testing.

10. What will happen if you decide to stop being in this study?

You can remove your child from the study or your child can decide to withdrawal at any time. You can either tell the research assistant working with you at ANY time during Part 1 or 2 of the study or you can call Principal Investigator Bruce Compas, Ph.D. at 615-322-8306.

11. Who to call for any questions or in case you are injured:

If you have any questions about this research study or if you feel your child has been hurt by being in this study, please feel free to contact Project Coordinator Laura Keys, M.S. at 615-343-8720 or Principal Investigator Bruce E. Compas, Ph.D. at 615-322-8306.

For additional information about giving consent or your rights as a person in this study, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273, or email at http://mcapps01.mc.vanderbilt.edu/IRB/WkshpReg.nsf/Suggestion Form?OpenForm.

14. Confidentiality:

All reasonable efforts will be made to keep the personal information in your research record private and confidential but absolute confidentiality cannot be guaranteed. Your information may be shared with institutional and/or governmental authorities, such as the Vanderbilt University Institutional Review Board and the Federal Government Office for Human Research Protections; however, they have their own policies and guidelines to assure that all reasonable efforts will be made to keep your child's personal health information private and confidential.

The study results will be retained in your child's research record for at least six years after the study is completed. A decision to not participate in this research study will not affect your child's treatment, payment or enrollment in any health plans or affect your eligibility for benefits. You will receive a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS STUDY

Please

[ ] I have read this consent form and all my questions have been answered.

[ ] The information in this consent form has been explained to me and all my questions have been answered.

[ ] I freely and voluntarily choose to participate in this study. I understand that I may withdraw at any time.

[ ] I freely and voluntarily choose to take part only in Part I of this study (psychological testing and completing questionnaires).

[ ] I freely and voluntarily choose for my child to take part in Part II of this study (brain imaging study).

[ ] I freely and voluntarily choose to allow my child participate in this study. I understand that my child may withdraw at any time and I may withdraw my child at any time.

[ ] I freely and voluntarily choose to allow the research team to contact me by telephone or mail about future research studies examining psychological issues in children and adolescents

_____ _____

Date Signature of volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title

This assent document applies to children 10-17 years old.

Name of participant _____ Age_____

Below are the answers to some of the questions you may have. If you have any questions about what is written below or have any other questions about this research, please ask them. You will be given a copy of this consent form.

1. Why are you doing this research?

We are interested in studying how kids' and teens' thinking changes as they get older. All kids are different in how their brains develop, and we want to see how brain development is connected to how they learn and remember new things, how they solve problems, and how they deal with their feelings. In addition to healthy kids like you, we are also asking people who were treated for cancer when they were young to participate in this study to see if the treatment they got has any effect on their thinking and learning.

2. What will I do and how long will it take?

We are asking you to take some skills tests. This will take about 3 ½ hours. We are also asking you to take some tests while you are in a machine that is able to take pictures of your brain. This is called "brain imaging." The machine will take pictures to show how your brain works while you take the tests and while you watch some short movie scenes. The movie scenes might be a little bit scary. This second part of the study takes about 3 hours.

As a thank-you for participating, you will get $25 for taking the skills tests and another $40 for doing the second part of the study where we use a machine to take pictures of your brain.

3. Do I have to be in this research study and can I stop if I want to?

You can choose whether or not you want to be in this research study. You can also stop at ANY time. You can skip a question or a test if you want to and nobody will be mad at you. You can also choose to do just one part of the study.

4. Could it make me sick?

No, but sometimes testing can be a little tiring or difficult. You can take breaks between tests if you start feeling tired or frustrated.

5. Will anyone know that I am in this research study?

No. Your answers will be kept private. Only the people working on our study will see your tests and forms. Your name will not be on any of the tests.

6. How will this research help me or other people?

This research will help us figure out how kids and teens learn and think. In the future it could help people who have learning and other school-related problems.

7. Who do I talk to if I have questions?

If you have any questions about this research study, you can call the Project Coordinator Laura Keys (615) 343-8720 or the Principal Investigator Dr. Bruce Compas (615) 322-8306.

[ ] **I would like to do Part I of this study (skills tests).**

[ ] **I would like to do Part II for this study (brain imaging).**

Date	Signature of volunteer

Assent obtained by:

Signature	Printed Name and Title

Appendix D

Sample Letters Recruiting Healthy Control Participants

Sample Letter Mentioning ALL Participant's Name and Cancer Treatment

Date

Name
Address

Dear <name>:

We are writing to invite you and your child to participate in a study of child development being conducted by the Department of Psychology and Human Development at Vanderbilt University. Your child was nominated for this study by <name of patient>. <Name of patient> is participating in this study because <he/she> was treated for cancer as a child. The purpose of the study is to help determine if there are long-term effects of cancer treatment on attention, memory, problem solving skills, and managing emotions. It is important that we are able to compare children and teenagers who have had cancer with those who have not had cancer. Your participation would be as part of the group of children and teenagers in the study who have not had cancer.

Participation in the study involves coming to the Department of Psychology and Human Development twice. During the first visit you and your child would complete several questionnaires and your child would take several brief tests of memory, attention, and problem-solving skills. This session would take approximately 90 minutes and you and your child would receive $25 as a token of our appreciation for your participation. Your child would then participate in a second session at Vanderbilt in which they would respond to similar tests of memory, attention, and problem solving while pictures of their brain are taken in a neuroimaging scanner. This session would take approximately 90 minutes and your child would again receive $25.

If you are interested in participating in this study or in learning more about the study please call 615-343-8720 and ask for Laura Keys or email Laura Keys at laura.l.keys@vanderbilt.edu.

Sincerely,

Bruce E. Compas, Ph.D.
Patricia and Rodes Hart Professor

Laura L. Keys, M.A..
Doctoral Student

Sample Letter Not Mentioning Cancer Treatment

Date

Name
Address

Dear <name>:

We are writing to invite you and your child to participate in a study of child development being conducted by the Department of Psychology and Human Development at Vanderbilt University. Your child was nominated for this study by <name of patient>, who is currently participating in this study. The purpose of the study is to examine attention, memory, problem solving skills, and managing emotions in adolescents.

Participation in the study involves coming to the Department of Psychology and Human Development twice. During the first visit you and your child would complete several questionnaires and your child would take several brief tests of memory, attention, and problem-solving skills. This session would take approximately 90 minutes and you and your child would receive $25 as a token of our appreciation for your participation. Your child would then participate in a second session at Vanderbilt in which they would respond to similar tests of memory, attention, and problem solving while pictures of their brain are taken in a neuroimaging scanner. This session would take approximately 90 minutes and your child would again receive $25.

If you are interested in participating in this study or in learning more about the study please call 615-343-8720 and ask for Laura Keys or email Laura Keys at laura.l.keys@vanderbilt.edu.

Sincerely,

Bruce E. Compas, Ph.D.
Patricia and Rodes Hart Professor

Laura L. Keys, M.S.
Doctoral Student

Sample Anonymous Letter

Date

Name
Address

Dear <name>:

We are writing to invite you and your child to participate in a study of child development being conducted by the Department of Psychology and Human Development at Vanderbilt University. Your child was nominated for this study by a classmate who is currently participating in this study. The purpose of the study is to examine attention, memory, problem solving skills, and managing emotions in adolescents.

Participation in the study involves coming to the Department of Psychology and Human Development twice. During the first visit you and your child would complete several questionnaires and your child would take several brief tests of memory, attention, and problem-solving skills. This session would take approximately 90 minutes and you and your child would receive $25 as a token of our appreciation for your participation. Your child would then participate in a second session at Vanderbilt in which they would respond to similar tests of memory, attention, and problem solving while pictures of their brain are taken in a neuroimaging scanner. This session would take approximately 90 minutes and your child would again receive $25.

If you are interested in participating in this study or in learning more about the study please call 615-343-8720 and ask for Laura Keys or email Laura Keys at laura.l.keys@vanderbilt.edu.

Sincerely,

Bruce E. Compas, Ph.D.
Patricia and Rodes Hart Professor

Laura L. Keys, M.S.
Doctoral Student

Appendix E

Advertisement for Recruiting Healthy Control Participants

Neurocognitive Development in Children and Adolescents Study

Children, adolescents, and young adults between the ages of 10 and 20 are needed for a research project to help us better understand the development of learning, memory, and problem-solving skills. We are also interested in how these areas of thinking are related to the ways in which young people handle stress and their emotions. There are two parts to this study which require two separate visits to Vanderbilt University Medical Center. The first part involves completing questionnaires and taking several tests of learning, memory, and problem-solving. The second part involves having images taken of your child's brain in a magnetic resonance scanner (MRI) while performing certain skills tests and watching two scenes from a movie. This will help us understand which parts of the brain are involved in the development of thinking and ability to handle emotions. Participants can choose to be in one or both parts of the study.

Compensation of $25 each for the young participant and parent is provided for the first part of the study. For the second part of the study, the young participant will be compensated $40. Parents will also be compensated an additional $10 to help with the cost of travel.

Interested individuals should contact:
Laura Keys, M.S. by telephone: (615) 343-8720 or email: laura.l.keys@vanderbilt.edu

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